Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende trifluridin/tipiracil til behandling af voksne patienter med metastatisk kræft i mavesæk og mavemund (adenokarcinom) efter mindst to tidligere behandlinger for fremskreden sygdom

Vers. 1.0

Bilagsoversigt

1. Medicinrådets sundhedsøkonomiske afrapportering vedr. trifluridin version 1.0
2. Forhandlingsnotat fra Amgros vedr. Trifluridin_tipiracil (Lonsurf)
3. Høringssvar fra ansøger
4. Medicinrådets vurdering vedr. trifluridin/tipiracil som monoterapi til behandling af voksne patienter med metastatisk kræft i mavesæk og mavemund (adenokarcinom) efter mindst to tidligere behandlinger for fremskreden sygdom
5. Ansøgers endelige ansøgning
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Medicinrådet

Medicinrådets sundheds-økonomiske afrapportering

Trifluridin/tipiracil

Metastatisk kræft i mavesæk og mavemund

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner. Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som standardbehandling, og udarbejder fælles regionale behandlingsvejledninger. Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

Dokumentets formål

Den sundhedsøkonomiske analyse indeholder Medicinrådets vurdering af de inkrementelle omkostninger pr. patient og budgetkonsekvenserne ved anbefaling. Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette bliver sammenfattet i Medicinrådets anbefaling vedr. lægemidlet.

Den sundhedsøkonomiske analyse er udarbejdet efter *Metodevejledning for omkostningsanalyse af nye lægemidler og indikationsudvidelser i hospitalssektoren*.

Dokumentoplysninger	
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Indholdsfortegnelse

1. Begreber og forkortelser

AIP	Apotekernes indkøbspris
BSA	Kropsoverfladeareal (*body surface area*)
BSC	*Best supportive care*
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
KM	Kaplan-Meier
OS	Samlet overlevelse (*overall survival*)
PFS	Progressionsfri sygdom (*progression-free survival*)
SAIP	Sygehusapotekernes indkøbspris
ToT	Tid i behandling (*time on treatment*)

2. Konklusion

Inkrementelle omkostninger og budgetkonsekvenser
I det scenarie, Medicinrådet mener er mest sandsynligt, er de inkrementelle omkostninger for trifluridin/tipiracil ca. [redacted] DKK pr. patient sammenlignet med *best supportive care* (BSC). Når analysen er udført med apotekernes indkøbspris (AIP), er de inkrementelle omkostninger til sammenligning ca. 83.000 DKK pr. patient.

De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostningerne for trifluridin/tipiracil. Derfor har den relative dosisintensitet for trifluridin/tipiracil nogen betydning for analysens resultat.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af trifluridin/tipiracil som mulig standardbehandling vil være ca [redacted] DKK i det femte år efter en anbefaling. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 4,1 mio. DKK i det femte år.

3. Introduktion

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af trifluridin/tipiracil som mulig standardbehandling på danske hospitaler til metastatisk kræft i mavesæk og mavemund.

Analysen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Servier. Medicinrådet modtog ansøgningen den 8. juni 2021.

3.1 Patientpopulation

Kræft i mavesæk (ventrikel), mavemund (gastroesophageal overgang) og spiserør (esophagus) hører samlet til den 8. hyppigste kræftform i Danmark. Medianalderen for diagnosetidspunktet er for alle tre kræftformer omkring 70 år. Fagudvalget skønner, at ca. 300 patienter pr. år vil modtage 1. linje, systemisk behandling med kombinationskemoterapi. Af patienter behandlet med kemoterapi med palliativt sigte er 31 % i live 1 år efter start på første systemiske behandling, ganske få er i live efter 5 år. Fagudvalget anslår, at under 50 patienter årligt kandiderer til behandling med trifluridin/tipiracil [1].

Yderligere information om sygdomsområdet kan findes i Medicinrådets vurderingsrapport.

3.1.1 Komparator

Medicinrådet har vurderet den kliniske værdi af trifluridin/tipiracil på baggrund af følgende kliniske spørgsmål:

Hvilken værdi har trifluridin/tipiracil sammenlignet med eksisterende standardbehandling til behandling af patienter med metastatisk kræft i mavesæk og mavemund (adenokarcinom), som tidligere er blevet behandlet med mindst to forudgående systemiske behandlingsregimer for fremskreden sygdom?

4. Vurdering af den sundhedsøkonomiske analyse

I sin ansøgning har ansøger indsendt en sundhedsøkonomisk analyse, der består af en omkostningsanalyse og en budgetkonsekvensanalyse. I omkostningsanalysen estimeres de inkrementelle omkostninger pr. patient for trifluridin/tipiracil sammenlignet med *best supportive care* (BSC). Medicinrådet vurderer nedenfor den sundhedsøkonomiske analyse, som ansøger har indsendt.

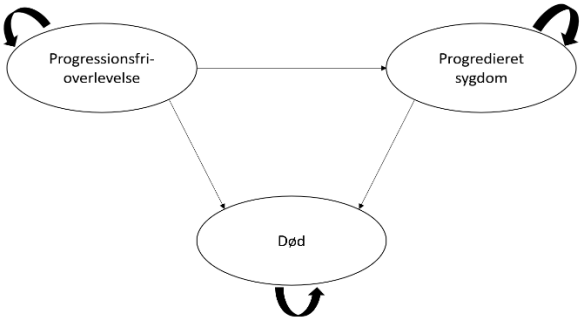
4.1 Antagelser og forudsætninger for modellen

Sammenligningen med BSC er lavet på baggrund af data fra TAGS-studiet [2], som også udgør datagrundlaget i Medicinrådets vurderingsrapport. TAGS er et randomiseret, placebo-kontrolleret fase-III-studie, som havde til formål at evaluere effekt og sikkerhed ved behandling med trifluridin/tipiracil sammenlignet med placebo (begge arme i kombination med BSC), til tidligere behandlede patienter med metastatisk mavekræft. Ansøger antager, at data fra placeboarmen i TAGS-studiet kan anvendes som proxy for den definerede komparator jf. protokollen vedr. trifluridin/tipiracil: bedste understøttende pleje (palliativ behandling), svarende til BSC.

4.1.1 Modelbeskrivelse

Ansøger har indsendt en *partitioned survival* model til at estimere omkostningerne forbundet med behandlingen med trifluridin/tipiracil. Modellen har en cykluslængde på én uge.

Modellen indeholder tre sygdomsstadier, som patienterne skifter mellem i takt med sygdomsprogression. De tre stadier i ansøgers model er 1) progressionsfri overlevelse, 2) post-progression og 3) stadiet død. Se figur 1 for de forskellige sygdomsstadier, og hvordan patienten kan bevæge sig mellem dem.



Figur 1. Beskrivelse af modelstrukturen i omkostningsanalysen

Alle patienter starter i sygdomsstadiet progressionsfri overlevelse, hvorfra deres bevægelse gennem modellen bestemmes ud fra ekstrapoleret forløbsdata. Patientens tid i stadiet progressionsfri overlevelse bestemmes ud fra data for progressionsfri overlevelse (PFS) fra studiet TAGS-studiet. Fra progressionsfri overlevelse kan patienten bevæge sig videre til stadiet post-progression og til stadiet død.

Patienter, der er progredieret, men ikke døde, vil befinde sig i post-progression. Tiden, patienterne befinder sig i i dette stadie, estimeres ud fra PFS- og OS-data fra TAGS-studiet som den andel af patienter, der hverken er i præ-progression eller død. Fra post-progression kan patienten udelukkende bevæge sig til det absorberende stadie død.

Andelen af patienter i stadiet død bliver estimeret ud fra OS-data TAGS-studiet.

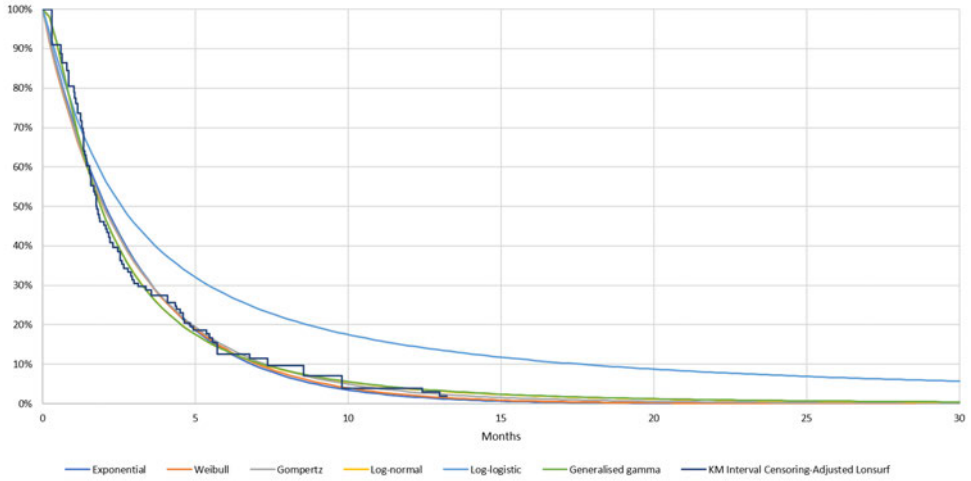
Medicinrådets vurdering af ansøgers model
Medicinrådet accepterer ansøgers tilgang vedr. ansøgers model.

4.1.2 Modelantagelser og -beskrivelse

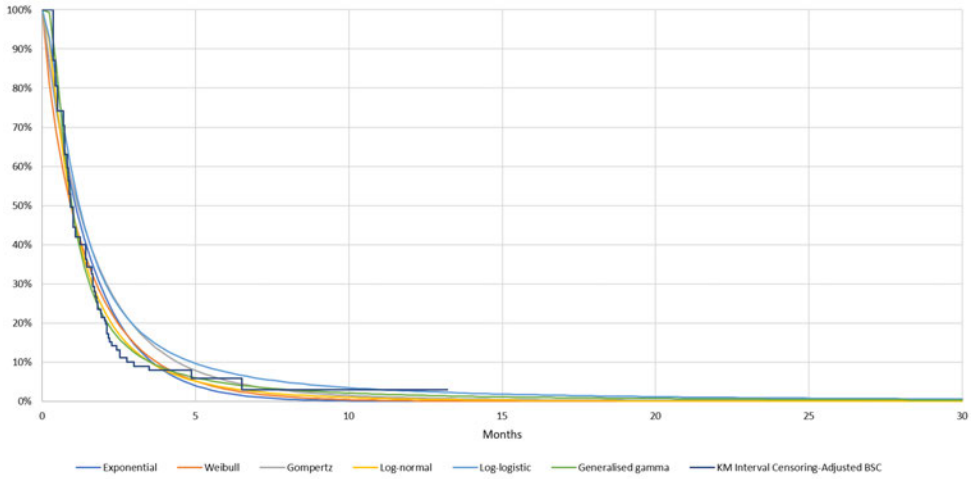
Ansøger modellerer tiden i de forskellige stadier ved at anvende ekstrapolerede Kaplan-Meier (KM)-data for PFS og OS. Dette er nødvendigt, da opfølgningen i TAGS-studiet er kortere end den anvendte tidshorisont.

Til at estimere PFS anvender ansøger en statistisk metode, *interval censoring adjustment*. Metoden anvendes, da der inden for de første 8 uger efter opstart af behandling i TAGS-studiet, var en stor andel af patienterne, der var progredieret i både trifluridin/tipiracil-armen og BSC-armen. I studiet kom patienterne første gang til kontrol efter 8 uger. Da progression først registreres ved kontrolbesøg, vurderer ansøger, at det er mest sandsynligt, at nogle patienter var progredieret tidligere end kontrolbesøget. Dette opfanges ikke i data. Ansøger anvender derfor *interval censoring adjustment*-metoden for at justere for denne overestimering af PFS.

Ansøger anvender log-normal som parametrisk funktion til at ekstrapolere det observerede PFS-data for både trifluridin/tipiracil og BSC, se figur 2 og figur 3.

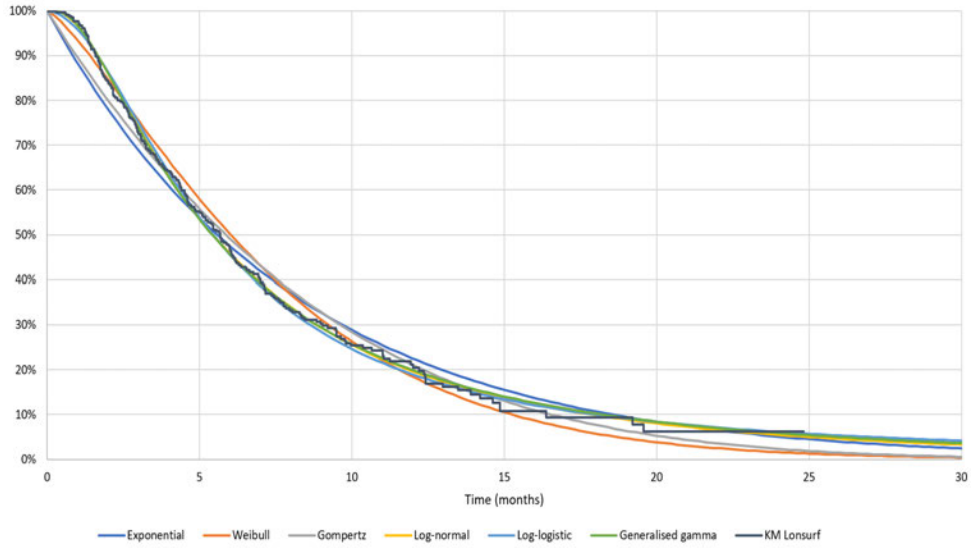


Figur 2. PFS-kurve for trifluridin/tipiracil

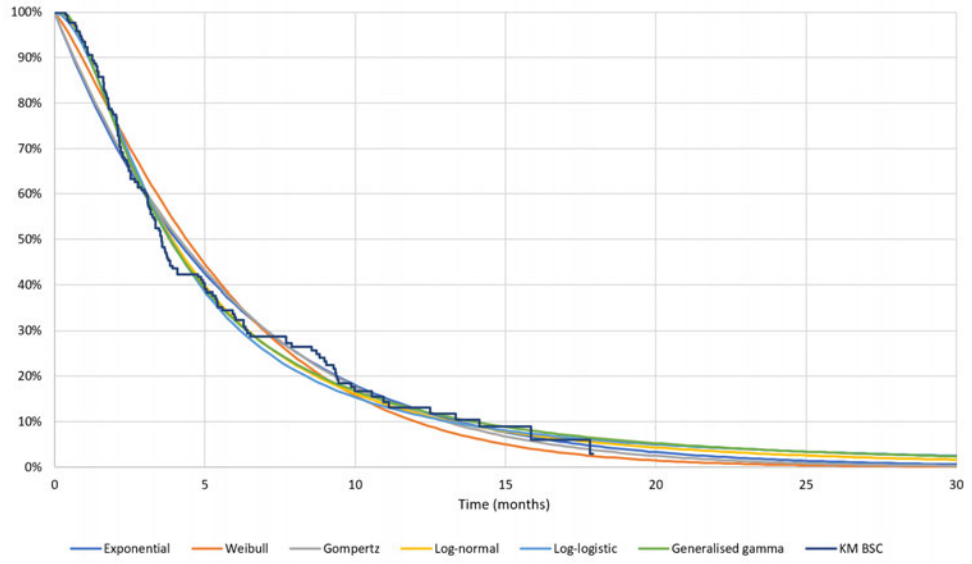


Figur 3. PFS-kurve for BSC

Til at ekstrapolere det observerede OS-data anvender ansøger log-normal som parametrisk funktion for både trifluridin/tipiracil og BSC, se figur 4 og figur 5. Ansøger har valgt de parametriske funktioner, der anvendes til ekstrapolering af PFS og OS, da ansøger argumenterer for, at funktionen har det bedste statistiske fit på KM-data.

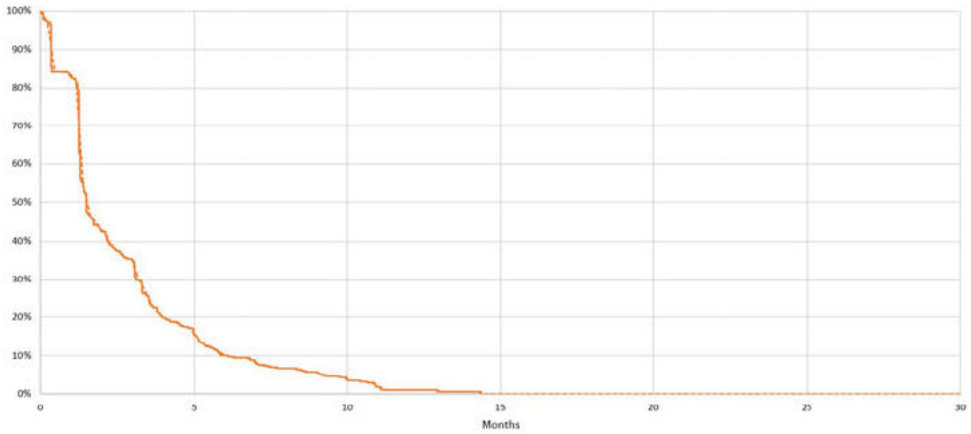


Figur 4. OS-kurve for trifluridin/tipiracil



Figur 5. OS-kurve for BSC

Ansøger har estimeret tiden i behandling (ToT) for trifluridin/tipiracil på baggrund af KM-data, se figur 6. Det har ikke været nødvendigt at ekstrapolere på data, da alle patienter afsluttede deres behandling i studiets opfølgningstid.



Figur 6. ToT-kurve for trifluridin/tipiracil

Medicinrådets vurdering af ansøgers modelantagelser

Medicinrådet vurderer, at ansøgers tilgang til estimering af PFS med brug af *interval censoring adjustment* er acceptabel. Ansøger har ikke vurderet PFS- og OS-kurvernes kliniske plausibilitet, men kun valgt parametriske funktioner til ekstrapolering af PFS og OS ud fra det bedste statistiske fit. Fagudvalget vurderer, at de ekstrapolerede PFS-kurver og OS-kurver for trifluridin/tipiracil og BSC overordnet virker rimelige. Fagudvalget bemærker yderligere, at der er minimal forskel på kurveforløbene på nær PFS log-logistic-kurven for trifluridin/tipiracil. Denne kurve vurderes dog at være urealistisk, da den viser, at nogle patienter vil være i live efter 30 måneder. Medicinrådet undersøger betydningen af valget af parametrisk funktion for analysens resultat ved at præsentere en følsomhedsanalyse, hvor Weibull-funktionen anvendes til ekstrapolering af OS for både trifluridin/tipiracil og BSC. Denne kurve repræsenterer det mest pessimistiske kurveforløb efter ca. 12 måneder.

Medicinrådet accepterer ansøgers estimater for behandlingsvarighed. Estimaterne for den gennemsnitlige ToT, PFS og OS, der er estimeret ud fra ekstrapoleret KM-data, er præsenteret i tabel 1.

Tabel 1. Gennemsnitlig tid i behandling, tid til progression og samlet overlevelse

Behandling	ToT [måneder]	PFS [måneder]	OS [måneder]
Trifluridin/tipiracil	3,4	3,4	8,3
BSC	Ikke relevant	2,1	6,1

*Tid i behandling (ToT), progressionsfri overlevelse (PFS), samlet overlevelse (OS).

Medicinrådet accepterer ansøgers tilgang vedr. modelantagelser, men præsenterer en følsomhedsanalyse, hvor Weilbull anvendes som parametrisk funktion til at ekstrapolere det observerede OS-data for trifluridin/tipiracil og BSC.

4.1.3 Analyseperspektiv

I overensstemmelse med Medicinrådets metoder har ansøger valgt et begrænset samfundsperspektiv til sin analyse. Analysen har en tidshorisont på 10 år, hvilket ansøger argumenterer for er en passende tidshorisont, da patienterne forventes at være døde inden for 10 år.

I overensstemmelse med Medicinrådets metodevejledning er omkostninger, der ligger efter det første år, diskonteret med en rate på 3,5 % pr. år.

Medicinrådets vurdering af ansøgers analyseperspektiv
Medicinrådet accepterer ansøgers valg vedr. analyseperspektiv.

4.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af trifluridin/tipiracil sammenlignet med BSC. Ansøger har inkluderet lægemiddelomkostninger, hospitalsomkostninger, omkostninger til efterfølgende behandling og patientomkostninger.

4.2.1 Lægemiddelomkostninger

Trifluridin/tipiracil er en oral behandling, og dosis er 35 mg/m^2 to gange dagligt på dag 1-5 og dag 8-12 i 28-dages cyklusser. Det gennemsnitlige kropsfladeareal (BSA) fra TAGS-studiet var på 1,78 m^2. Ansøger anvender fordelingen af BSA fra TAGS-studiet til at estimere lægemiddelomkostningerne, se tabel 2.

Tabel 2: Fordeling over antal mg pr. administration

mg pr. administration	Andel af patienter
35	0,3 %
40	2,4 %
45	10,6 %
50	24,8 %
55	31,2 %
60	21,2 %
65	7,7 %
70	1,5 %
75	0,2 %

Behandlingen med trifluridin/tipiracil ophøres ved sygdomsprogression eller ved

intolerable bivirkninger. Ved svære bivirkninger kan patienterne dosisreduceres til minimum 20 mg/m^2 to gange dagligt. Det er ikke muligt at øge dosis igen efter en dosisreduktion jf. produktresuméet. Den relative dosisintensitet for trifluridin/tipiracil i TAGS-studiet var 0,847, og ansøger anvender denne dosisintensitet i analysen. Ansøger antager, at det ikke er muligt at dele pakninger og tabletter mellem patienter.

Ansøger har, jf. *Metodevejledning for omkostningsanalyser af nye lægemidler og indikationer i hospitalssektoren,* estimeret lægemiddelomkostninger på baggrund af apotekernes indkøbspris (AIP).

Medicinrådets vurdering af ansøgers antagelser vedr. lægemiddelomkostninger
Fagudvalget vurderer, at fordelingen af antal mg pr. administration for patienterne i TAGS-studiet sandsynligvis svarer til fordelingen, man vil se i dansk praksis. Fagudvalget vurderer også, at det er rimeligt at anvende den relative dosisintensitet fra TAGS-studiet, men pointerer, at der er usikkerhed omkring den reelle dosisintensitet i dansk praksis. Medicinrådet undersøger derfor betydningen af den relative dosisintensitet for analysens resultat ved at præsentere en følsomhedsanalyse, hvor det antages, at ingen patienter dosisreduceres. Medicinrådet har udskiftet AIP med sygehusapotekernes indkøbspris (SAIP), se tabel 2.

Tabel 3. Anvendte lægemiddelpriser, SAIP (juni 2021)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Trifluridin/tipiracil	15 mg + 6,14 mg	20 stk.	[redacted]	Amgros
Trifluridin/tipiracil	15 mg + 6,14 mg	60 stk.	[redacted]	Amgros
Trifluridin/tipiracil	20 mg + 8,19 mg	20 stk.	[redacted]	Amgros
Trifluridin/tipiracil	20 mg + 8,19 mg	60 stk.	[redacted]	Amgros

Medicinrådet accepterer ansøgers valg vedr. lægemiddelomkostninger, men præsenterer en følsomhedsanalyse hvor den relative dosisintensitet sættes til 1 (ingen patienter dosisreduceres).

4.2.2 Hospitalsomkostninger

Ansøger har inkluderet omkostninger til opstart af behandling med trifluridin/tipiracil, monitoreringsomkostninger og bivirkningsomkostninger.

Opstart af behandling

Trifluridin/tipiracil er en oral behandling, og ansøger har derfor ikke inkluderet administrationsomkostninger udover omkostninger til opstart af behandlingen. Ansøger antager, at patienter opstarter behandling hos en sygeplejerske, og anvender derfor en omkostning for en sygeplejerskes timeomkostning på 554 DKK jf. *Medicinrådets værdisætning af enhedsomkostninger.*

Medicinrådets vurdering af ansøgers antagelser vedr. opstart af behandling
Ifølge fagudvalget vil det være en læge, der opstarter behandling med trifluridin/tipiracil, og dette understøttes af produktresuméet for trifluridin/tipiracil. Medicinrådet anvender derfor omkostningen for en læges timeomkostning på 1.316 DKK jf. *Medicinrådets værdisætning af enhedsomkostninger* i stedet for omkostningen for en sygeplejerske. Denne ændring vurderes at have minimal betydning for analysens resultat.

Medicinrådet anvender omkostningen for en læge til opstart af behandling med trifluridin/tipiracil i stedet for omkostningen for en sygeplejerske.

Monitoreringsomkostninger

Ansøger har inkluderet forskellige monitoreringsomkostninger afhængigt af om patienterne modtager trifluridin/tipiracil eller BSC. For patienter, der er i behandling med trifluridin/tipiracil antager ansøger, at patienterne hver måned skal have en lægekonsultation á 30 minutter, fuld blodtælling, test af nyrefunktion og test af leverfunktion og hver tredje måned en CT-scanning. Når patienterne stopper behandling, antages det, at de skal til en lægekonsultation hver tredje måned. For patienter, der modtager BSC, antager ansøger, at de har en lægekonsultation hver tredje måned, da de ikke er i aktiv behandling.

Medicinrådets vurdering af ansøgers antagelser vedr. monitoreringsomkostninger
Fagudvalget vurderer, at man i dansk klinisk praksis vil CT-scanne patienter, der får trifluridin/tipiracil hver anden måned i stedet for hver tredje måned, da patienterne hurtigt progredierer. Dette ændrer Medicinrådet derfor i egen hovedanalyse, se tabel 3. Denne ændring har minimal betydning for analysens resultat. Ifølge fagudvalget er der usikkerhed omkring monitoreringen ved BSC, og i mangel på bedre estimater accepteres ansøgers antagelser.

Tabel 4: Monitorering under og efter behandling med trifluridin/tipiracil og ved BSC

	Frekvens	Omkostning [DKK]	Kilde
Monitorering under behandling med trifluridin/tipiracil			
Lægekonsultation á 30 min.	Hver måned	658	Medicinrådets værdisætning af enhedsomkostninger
CT-scanning	Hver 2. måned	2.007	DRG 2021: 30PR06
Blodtælling	Hver måned	129	Prisliste for rutineanalyser KBA Bispebjerg Hospital, 2021
Test af nyrefunktion	Hver måned	114	Prisliste for rutineanalyser KBA Bispebjerg Hospital, 2021
Test af leverfunktion	Hver måned	62	Prisliste for rutineanalyser KBA Bispebjerg Hospital, 2021

	Frekvens	Omkostning [DKK]	Kilde
Monitorering efter behandling med trifluridin/tipiracil			
Lægekonsultation á 30 min.	Hver tredje måned	658	Medicinrådets værdisætning af enhedsomkostninger
Monitorering ved BSC			
Lægekonsultation á 30 min.	Hver tredje måned	658	Medicinrådets værdisætning af enhedsomkostninger

Medicinrådet accepterer ansøgers tilgang vedr. monitoreringsomkostninger, men ændrer frekvensen for CT-scanninger for patienter, der behandles med trifluridin/tipiracil.

Bivirkningsomkostninger

Ansøger har inkluderet omkostninger forbundet med bivirkninger af grad 3-4 for trifluridin/tipiracil og BSC og benytter de rapporterede bivirkningsrater fra TAGS-studiet. Ansøger estimerer omkostninger forbundet med behandling af bivirkningerne ved brug af DRG 2021.

Medicinrådets vurdering af ansøgers antagelser vedr. bivirkningsomkostninger

Medicinrådet accepterer ansøgers tilgang til estimering af bivirkningsomkostninger. Bivirkningsfrekvenser og anvendte takster kan ses i tabel 4.

Tabel 5. Rapporterede bivirkningsfrekvenser ved behandling med trifluridin/tipiracil og BSC samt enhedsomkostninger for bivirkningerne

	Trifluridin/tipiracil	BSC	Omkostning [DKK]	DRG
Anæmi	11,0 %	3,0 %	6.042	16PR01
Neutropeni	23,0 %	0,0 %	35.483	16MA03
Leukopeni	6,9 %	0,0 %	35.483	16MA03
Mavesmerter	0,3 %	0,6 %	22.789	06MA14
Fatigue	3,0 %	1,2 %	6.016	23MA05
Asteni	0,9 %	1,2 %	6.016	23MA05
Generelt forringet helbred	0,3 %	0,0 %	6.016	23MA05
Nedsat neutrofiltal	11,0 %	0,0 %	35.483	16MA03
Nedsat appetit	3,0 %	1,8 %	6.016	23MA05

Medicinrådet accepterer ansøgers tilgang vedr. bivirkningsomkostninger.

4.2.3 Efterfølgende behandling og terminale omkostninger

Ansøger inkluderer omkostninger til efterfølgende behandling, efter patienter har progredieret på trifluridin/tipiracil eller BSC. Ansøgers analyse indeholder fire mulige efterfølgende behandlinger: 1) operation, 2) stråleterapi, 3) docetaxel monoterapi og 4) docetaxel i kombination med ramucirumab. Ansøger antager, at andelen af patienter, der modtager de forskellige behandlinger, afhænger af, om patienterne har fået trifluridin/tipiracil eller BSC.

Ansøger har inkluderet terminale omkostninger i modellen. Da alle patienter dør i modellen, er forskelle i terminale omkostninger derfor udelukkende drevet af forskelle i diskontering, der afhænger af tidspunktet for død. Ansøger anvender en enhedsomkostning på 88.471 DKK (DRG 2021: 26MP45: Specialiseret Palliativ indsats, Stor) for terminale omkostninger.

Medicinrådets vurdering af ansøgers antagelser vedr. efterfølgende behandling
Ifølge fagudvalget vil langt størstedelen af patienterne ikke modtage efterfølgende behandling, men blive tilknyttet et palliativt team. Enkelte patienter vil blive tilbudt efterfølgende behandling, som regel i form af stråleterapi, men behandlingen og andelen vil være ens uanset, om de tidligere har fået trifluridin/tipiracil eller BSC. Derudover påpeger fagudvalget, at ramucirumab ikke anvendes i dansk praksis. Medicinrådet ekskluderer derfor omkostninger til efterfølgende behandling i egen hovedanalyse. Ændringen har minimal betydning for analysens resultat.

Fagudvalget vurderer, at langt størstedelen af patienter bliver tilknyttet et palliativt team efter progression. Der er dog stor usikkerhed forbundet med den behandling patienterne modtager, og om der vil være forskel på behandlingen mellem patienter. Medicinrådet accepterer ansøgers antagelser vedrørende terminale omkostninger og præsenterer en følsomhedsanalyse, hvor de terminale omkostninger ekskluderes.

Medicinrådet accepterer ikke ansøgers tilgang vedrørende efterfølgende behandling, og ekskluderer omkostningerne i Medicinrådets hovedanalyse. Medicinrådet accepterer ansøgers antagelse vedr. terminale omkostninger, og præsenterer en følsomhedsanalyse, hvor de terminale omkostninger ekskluderes.

4.2.4 Patientomkostninger

Ansøger estimerer patientomkostningerne på baggrund af administrations- og monitoreringsbesøg på hospitalet og pårørendes tid til at tage sig af patienten. Ansøger anvender en enhedsomkostning for pårørendes tid på 179 DKK pr. time og transportomkostninger på 100 DKK pr. besøg, jf. *Medicinrådets værdisætning af enhedsomkostninger*. Ansøger har kun inkluderet transportomkostninger, når patienten skal på hospitalet, men ikke omkostninger til patienttid.

Ansøger antager, at 50 % af patienterne har brug for hjælp og støtte fra pårørende. For disse patienter antager ansøger, at de pårørende i gennemsnit bruger ca. 2,4 arbejdsdage (ca. 18 timer) på at tage sig af patienten om ugen. Dette baserer ansøger på en engelsk spørgeundersøgelse [3].

Medicinrådets vurdering af ansøgers antagelser vedr. patientomkostninger
Ansøger har inkluderet transportomkostninger, men ikke omkostninger til tiden patienterne bruger, når de skal ind på hospitalet. Medicinrådet inkluderer disse omkostninger med antagelsen om, at patienterne i gennemsnit bruger en time pr. gang, når de skal ind på hospitalet. Denne ændring har lille betydning for analysens resultat.

Fagudvalget vurderer, at det er meget usikkert, hvor meget tid pårørende eventuelt bruger på hjælp til patienten, og hvor stor en andel af patienterne, der har brug for støtte. Dog vurderer fagudvalget, at ansøgers estimat for pårørendes tidsforbrug lyder for højt. Fagudvalget vurderer yderligere, at det er problematisk at anvende estimater for de pårørendes tidsforbrug fra andre lande, i dette tilfælde England. Medicinrådet ekskluderer derfor omkostninger til pårørendes tidsforbrug i Medicinrådets hovedanalyse. Ændringen har lille betydning for analysens resultat.

Medicinrådet ekskluderer omkostninger til pårørendes tidsforbrug, og inkluderer patientomkostninger, når patienten skal ind på hospitalet.

4.3 Følsomhedsanalyser

Formålet med følsomhedsanalyserne er at undersøge usikkerhederne i analysen og de økonomiske konsekvenser af at justere de parametre, der er usikre. Ansøger har udarbejdet en række følsomhedsanalyser, hvor betydningen af variation i forskellige parametre undersøges. Da ansøger har inkluderet efterfølgende behandling i alle følsomhedsanalyser, vælger Medicinrådet ikke at præsentere disse.

Medicinrådet vælger at præsentere en følsomhedsanalyse, hvor den parametriske funktion, Weibull, anvendes til at ekstrapolere OS for trifluridin/tipiracil og BSC. Weibull-funktionen repræsenterer en OS-kurve, der er mere pessimistisk efter ca. 12 måneder.

Medicinrådet præsenterer en følsomhedsanalyse, hvor det antages, at alle patienter, får fuld dosis, så længe de er i behandling. Det vil sige, at ingen dosisreduceres og den relative dosisintensitet sættes derfor til 1.

Medicinrådet præsenterer derudover en følsomhedsanalyse, hvor terminale omkostninger ekskluderes.

Medicinrådet vælger ikke at præsentere ansøgers følsomhedsanalyser. Medicinrådet præsenterer følsomhedsanalyser, hvor Weibull-funktionen anvendes til ekstrapolering af observeret OS-data, og hvor den relative dosisintensitet sættes til 1. Derudover præsenteres en følsomhedsanalyse, hvor terminale omkostninger ekskluderes.

4.4 Opsummering af basisantagelser

I tabel 5 opsummeres basisantagelserne i henholdsvis ansøgers og Medicinrådets hovedanalyse.

Tabel 6. Basisantagelser for ansøgers og Medicinrådets hovedanalyse

Basisantagelser	Ansøger	Medicinrådet
Tidshorisont	10 år	10 år
Diskonteringsrate	3,5 %	3,5 %
Inkluderede omkostninger	Lægemiddelomkostninger Hospitalsomkostninger Bivirkningsomkostninger Omkostninger til efterfølgende behandling Terminale omkostninger Patientomkostninger	Lægemiddelomkostninger Hospitalsomkostninger Bivirkningsomkostninger Terminale omkostninger Patientomkostninger
Relativ dosisintensitet	0,847	0,847
Gennemsnitlig behandlingslængde for trifluridin/tipiracil	3,4 måneder	3,4 måneder
Parametriske funktioner for PFS		
Trifluridin/tipiracil	Log-normal	Log-normal
BSC	Log-normal	Log-normal
Parametriske funktioner for OS		
Trifluridin/tipiracil	Log-normal	Log-normal
BSC	Log-normal	Log-normal
Inkludering af spild	Ja	Ja
Inkludering af pårørendes tidsforbrug	Ja	Nej
Inkludering af efterfølgende behandling	Ja	Nej

5. Resultater

5.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse med undtagelse af de væsentligste ændringer, der fremgår af tabel 5.

Den gennemsnitlige inkrementelle omkostning pr. patient bliver ca. [redacted] DKK i Medicinrådets hovedanalyse. Størstedelen af omkostningerne forekommer dog de første måneder af behandlingsforløbet.

Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient ca. 83.000 DKK.

Resultaterne fra Medicinrådets hovedanalyse er præsenteret i tabel 6.

Tabel 7. Resultatet af Medicinrådets hovedanalyse ved sammenligning med BSC, DKK, diskonterede tal

	Trifluridin/tipiracil	BSC	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	0	[redacted]
Hospitalsomkostninger	97.533	89.581	7.952
Patientomkostninger	4.308	2.707	1.601
Totale omkostninger	[redacted]	**92.288**	[redacted]

5.1.1 Resultatet af Medicinrådets følsomhedsanalyser

Ved samme antagelser som i Medicinrådets hovedanalyse for meromkostninger har Medicinrådet udført en følsomhedsanalyse på parametrene listet i tabel 7.

Tabel 8. Resultatet af Medicinrådets følsomhedsanalyse sammenlignet med hovedanalysen, DKK

Scenarie	Inkrementelle omkostninger
Resultatet af hovedanalysen	[redacted]
Weibull anvendes til ekstrapolering af OS	[redacted]
Den relative dosisintensitet sættes til 1	[redacted]
Terminale omkostninger ekskluderes	[redacted]

6. Budgetkonsekvenser

Budgetkonsekvenserne pr. år er baseret på antagelsen om, at trifluridin/tipiracil vil blive anbefalet som mulig standardbehandling. Man ser derfor på to scenarier:

- Trifluridin/tipiracil bliver anbefalet som mulig standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler.
- Trifluridin/tipiracil bliver ikke anbefalet som mulig standardbehandling.

Budgetkonsekvenserne udgør forskellen mellem de samlede omkostninger i de to scenarier.

6.1 Estimat af patientantal og markedsandel

Ansøger har antaget, at ca. 50 patienter kandiderer til behandling med trifluridin/tipiracil om året. Hvis trifluridin/tipiracil anbefales som standardbehandling, antager ansøger, at markedsoptaget vil være på 40 % i år 1 stigende til 100 % i år 4.

Medicinrådets vurdering af ansøgers budgetkonsekvensanalyse
Fagudvalget er enig i ansøgers antagelse om patientantal, men vurderer, at markedsoptaget for trifluridin/tipiracil vil være 90 % i år 1 og 100 % fra år 2, hvis trifluridin/tipiracil anbefales som standardbehandling, se tabel 8. Dette anslår fagudvalget, da lægemidlet er velkendt, og man forventer ikke, at der vil være udfordringer ift. implementeringen af den eventuelle nye praksis.

Tabel 9. Medicinrådets estimat af antal nye patienter pr. år

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Trifluridin/tipiracil	45	50	50	50	50
BSC	5	0	0	0	0
			Anbefales ikke		
Trifluridin/tipiracil	0	0	0	0	0
BSC	50	50	50	50	50

Medicinrådet ændrer markedsoptaget til 90 % i år 1 stigende til 100 % fra 2 år i det scenarie, at trifluridin/tipiracil anbefales som standardbehandling.

6.2 Medicinrådets budgetkonsekvensanalyse

Medicinrådet har korrigeret følgende estimater i sin budgetkonsekvensanalyse i forhold til ansøgers budgetkonsekvensanalyse:

- Markedsoptaget for trifluridin/tipiracil sættes til 90 % i år 1 og 100 % fra år 2, hvis lægemidlet anbefales.

Medicinrådet estimerer, at anvendelse af trifluridin/tipiracil vil resultere i budgetkonsekvenser på ca. [redacted] DKK i det femte år efter en anbefaling. Resultatet er præsenteret i tabel 9.

Er analysen udført med AIP, bliver budgetkonsekvenserne ca. 4,1 mio. DKK i år 5.

Tabel 10. Medicinrådets analyse af totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7. Diskussion

Behandling med trifluridin/tipiracil er forbundet med inkrementelle omkostninger på ca. [redacted] sammenlignet med behandling med BSC. De inkrementelle omkostninger er næsten udelukkende drevet af lægemiddelomkostningerne trifluridin/tipiracil.

Lægemiddelomkostningerne er estimeret ud fra KM-data. Alle patienter færdiggjorde behandling i TAGS-studiet, og det er derfor ikke nødvendigt at ekstrapolere på behandlingslængden. Ansøger anvender en relativ dosisintensitet på 0,847 fra TAGS-studiet. Det har nogen betydning for analysens resultat, om den relative dosisintensitet sættes til 1, dvs. at det antages, at alle patienter modtager fuld dosis, mens de er i behandling. De inkrementelle omkostninger stiger i dette scenarie fra ca. [redacted] DKK til ca [redacted] DKK

Fagudvalget vurderer, at OS-kurverne for trifluridin/tipiracil og BSC kan være overestimeret, særligt for andelen der i live efter omkring 20 måneder. En følsomhedsanalyse viser dog, at det har minimal betydning for analysens resultat, hvis Weibull-funktionen anvendes til ekstrapolering. Weibull-kurven repræsenterer en OS, der er mere pessimistisk i slutningen af kurveforløbet. Det har ligeledes minimal betydning for analysens resultat, om terminale omkostninger ekskluderes.

8. Referencer

1. Medicinrådets protokol for vurdering af trifluridin / tipiracil som monoterapi til behandling af voksne patienter med metastatisk kræft i mavesæk og mavemund (adenocarcinom) efter mindst to tidligere behandlinger for fremskreden sygdom. :1–18.

2. Shitara K, Doi T, Dvorkin M, Mansoor W, Arkenau HT, Prokharau A, et al. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2018;19(11):1437–48.

3. Picture TR. The rich picture of cancer carers. Tilgængelig fra: https://www.macmillan.org.uk/_images/carers-of-people-with-cancer_tcm9-282780.pdf

9. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	29. september 2021	Godkendt af Medicinrådet

10. Bilag

10.1 Resultatet af ansøgers hovedanalyse

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient ca. [redacted] DKK over en tidshorisont på 10 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i tabel 10.

Tabel 11. Resultatet af ansøgers hovedanalyse, DKK, diskonterede tal

	Trifluridin/tipiracil	BSC	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	95.732	89.581	6.151
Efterfølgende behandling	[redacted]	[redacted]	[redacted]
Patientomkostninger	21.829	16.045	5.785
Totale omkostninger	[redacted]	[redacted]	[redacted]

10.2 Resultatet af ansøgers budgetkonsekvensanalyse

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som er inkluderet i omkostningsanalysen, dog uden patientomkostninger.

Med ovenstående antagelser om patientantal og markedsandel estimerer ansøger, at anvendelse af trifluridin/tipiracil vil resultere i budgetkonsekvenser på [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af tabel 11.

Tabel 12. Ansøgers hovedanalyse for totale budgetkonsekvenser, mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Forhandlingsnotat

Dato for behandling i Medicinrådet	27.10.2021
Leverandør	Servier
Lægemiddel	Trifluridin/tipiracil (Lonsurf)
Ansøgt indikation	Trifluridin/tipiracil som monoterapi til behandling af voksne patienter med metastatisk kræft i mavesæk og mavemund (adenokarcinom) efter mindst to tidligere behandlinger for fremskreden sygdom.

Forhandlingsresultat

Lonsurf indgår i et eksisterende udbud. Amgros har derfor ikke forhandlet en ny aftale med Servier. Amgros har følgende pris på Trifluridin/tipiracil (Lonsurf):

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP	Nuværende SAIP	Rabatprocent ift. AIP
Trifluridin/tipiracil	15 mg + 6,14 mg	20 stk.	6.135,53	[redacted]	[redacted]
Trifluridin/tipiracil	15 mg + 6,14 mg	60 stk.	18.398,64	[redacted]	[redacted]
Trifluridin/tipiracil	20 mg + 8,19 mg	20 stk.	8.180,71	[redacted]	[redacted]
Trifluridin/tipiracil	20 mg + 8,19 mg	60 stk.	24.534,17	[redacted]	[redacted]

Trifluridin/tipiracil (Lonsurf) indgår for nuværende i et udbud, der løber fra 1. september 2020 til 31. marts 2022. [redacted]

Vurdering af forhandlingsresultatet

Der har ikke fundet en forhandling sted. [redacted]

Status fra andre lande

Trifluridin/tipiracil (Lonsurf) er på nuværende tidspunkt under vurdering i Norge.

NICE anbefaler ikke trifluridine/tipiracil (Lonsurf) til behandling af voksne patienter med metastatisk kræft i mavesæk og mavemund efter mindst to tidligere behandlinger for fremskreden sygdom. NICE mener ikke at deres kriterier som livsforlængende behandling ved livets slutning er mødt. Trifluridin/tipiracil anbefales ikke til brug indenfor Cancer Drugs Fund. [1]

[1] https://www.nice.org.uk/guidance/TA669/chapter/1-Recommendations

2021-10-06

Dokumentnummer: 122820

Medicinrådets vurdering vedrørende trifluridin/tipiracil som monoterapi til behandling af voksne patienter med metastatisk kræft i mavesæk og mavemund (adenokarcinom) efter mindst to tidligere behandlinger for fremskreden sygdom.

Response to the Danish Medicines Council (DMC) on their evaluation from September 1 and September 29, 2021.

Servier hereby acknowledge the receipt of the assessment report from Medicinrådet and for the opportunity to send a response for the hearing.

Servier has taken the assessment of added clinical value into consideration but would also like to note the following:

Servier disagrees with the degrading from the initial assessment of the overall survival (OS) and progression free survival (PFS) from moderate clinical added value to small added value in the final assessment. Servier finds that the moderate clinical added value can be argued as both the primary endpoint OS, as well as the secondary endpoint PFS reaches a significant difference versus the control arm. Even though the absolute difference does not live up to minimum clinically relevant difference (MKRF), Servier believes that the risk reduction is of major importance for this severe group of patients. Servier would also like to note the benefits seen in the subgroup with 3rd line data where the OS endpoint is above the MKRF.

Kind regards

Jan Wahlberg
Nordic Medical & Market Access Lead
Servier Nordics

Medicinrådet

Medicinrådets vurdering vedrørende trifluridin/tipiracil som monoterapi til behandling af voksne patienter med metastatisk kræft i mavesæk og mavemund (adenokarcinom) efter mindst to tidligere behandlinger for fremskreden sygdom

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser skal anbefales som mulig standardbehandling. Medicinrådet udarbejder også behandlingsvejledninger og rekommandationer for anvendelse af medicin på sygehusene. Derudover kan Medicinrådet tage andre typer sager op, der handler om medicinanvendelse.

Om vurderingsrapporten

Vurderingsrapporten indeholder Medicinrådets vurdering af, hvilken værdi lægemidlet har for patienten i forhold til nuværende standardbehandling.

Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette bliver sammenfattet i Medicinrådets anbefaling vedr. lægemidlet.

Lægemidlet er vurderet efter *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, som du kan finde på Medicinrådets hjemmeside under siden Metoder.

Dokumentoplysninger	
Godkendelsesdato	29.09.2021
Dokumentnummer	122820
Versionsnummer	1.0

Indholdsfortegnelse

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 29. september 2021

1. Medicinrådets konklusion

Medicinrådet vurderer, at trifluridin/tipiracil til behandling af voksne patienter med metastatisk kræft i mavesæk og mavemund (adenokarcinom), som har fået mindst to behandlinger for fremskreden sygdom, samlet har lille merværdi sammenlignet med lindrende behandling (best supportive care). Dog har behandlingen kun en marginal effekt og flere bivirkninger. Evidensens kvalitet vurderes at være lav.

MEDICINRÅDET KATEGORISERER LÆGEMIDLERS VÆRDI I EN AF FØLGENDE KATEGORIER:

- **Stor merværdi:** Der er påvist en stor forbedring i effektforhold i forhold til gældende standardbehandling, eksempelvis markant forbedret overlevelse, markant reduktion i forekomsten af alvorlige symptomer og/eller alvorlige bivirkninger.
- **Moderat merværdi:** Der er påvist en moderat forbedring i forhold til gældende standardbehandling, eksempelvis moderat forbedret overlevelse, moderat reduktion i forekomsten af symptomer og/eller bivirkninger.
- **Lille merværdi:** Der er påvist en lille forbedring i forhold til gældende standardbehandling, eksempelvis en dokumenteret forbedret overlevelse, en reduktion i forekomsten af symptomer og/eller bivirkninger.
- **Merværdi af ukendt størrelse:** Der er påvist en forbedring i forhold til gældende standardbehandling, men størrelsen af forbedring kan ikke bestemmes. Lægemidlets merværdi er som minimum lille, men kunne også være moderat eller stor.
- **Ingen dokumenteret merværdi:** Der er ikke påvist en merværdi i forhold til gældende standardbehandling. Omvendt tyder den tilgængelige evidens heller ikke på, at der er en negativ værdi.
- **Negativ værdi:** Der er påvist en negativ værdi i forhold til gældende standardbehandling.

I nogle situationer er det ikke muligt at kategorisere lægemidlets samlede værdi. De situationer opstår, når evidensgrundlaget for vurderingen er for usikkert til at kategorisere værdien jf. Medicinrådets metoder (fx på grund af usikkerheder omkring effektforhold og spinkelt datagrundlag). Medicinrådet konkluderer da, at samlet værdi ikke kan kategoriseres. Medicinrådet vil i disse tilfælde argumentere for, om der er grund til at formode, at det nye lægemiddel er dårligere eller evt. bedre end gældende standardbehandling, eller der ikke er grund til at skelne mellem behandlingerne. Det sker på baggrund af det foreliggende datagrundlag og fagudvalgets kliniske erfaring. Vurderingen er forbundet med større usikkerhed end vurderinger, hvor lægemidlets værdi kan kategoriseres.

MEDICINRÅDET VURDERER KVALITETEN AF DE DATA, DER LIGGER TIL GRUND FOR VURDERINGEN AF LÆGEMIDLET (EVIDENSENS KVALITET) I EN AF FØLGENDE GRADE-KATEGORIER:

- **Høj:** Nye studier vil med meget lav sandsynlighed ændre konklusionen.
- **Moderat:** Nye studier vil med lav sandsynlighed ændre konklusionen.
- **Lav:** Nye studier vil med moderat sandsynlighed ændre konklusionen.
- **Meget lav:** Nye studier vil med høj sandsynlighed ændre konklusionen.

2. Begreber og forkortelser

5-FU:	5-Fluoropyrimidin
BSC	*Best supportive care*
CI:	Konfidensinterval
DECV:	Dansk Esophagus Cardia Ventrikel
ECOG:	*Eastern Cooperative Oncology Group*
EMA:	*European Medicines Agency*
EORTC:	*European Organisation for Research and Treatment of Cancer*
EPAR:	*European public assessment reports*
ESMO:	European Society for Medical Oncology
G-CSF	Granulocytkoloni stimulerende vækstfaktor
GRADE:	Grading of Recommendations Assessment, Development and Evaluation System (system til vurdering af evidens)
HR:	Hazard ratio
MKRF:	Mindste klinisk relevante forskel
ORR:	Overall response rate
OS:	*Overall Survival* (samlet overlevelse)
PFS:	*Progression free survival* (progressionsfri overlevelse)
PICO:	Population, intervention, comparator, outcome
PS:	Performancestatus
QLQ-C30:	*Quality of Life Questionnaire-Core* (30 spørgsmål vedr. livskvalitet til patienter med kræft)
QLQ-STO22:	*Quality of Life Questionnaire-Stomach 22* (22 spørgsmål vedr. livskvalitet til patienter med kræft i mavesækken)
RR:	Relativ risiko
S1:	Dihydropyrimidine dehydrogenase (DPD) inhibitory fluoropyrimidine (DIF) based on a biochemical modulation of 5-fluorouracil (5-FU); S-1 contains tegafur (FF) and two types of enzyme inhibitor, 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo) in a molar ratio of 1:0.4:1.
SAE:	Serious adverse event

3. Introduktion

Formålet med Medicinrådets vurdering af trifluridin/tipiracil (Lonsurf®) som monoterapi til behandling af patienter med metastatisk kræft i mavesæk og mavemund (adenokarcinom) efter mindst to tidligere systemiske behandlinger for fremskreden sygdom er, at vurdere den værdi lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Servier. Medicinrådet modtog ansøgningen den 8. juni 2021.

Det kliniske spørgsmål er:

Hvilken værdi har trifluridin/tipiracil sammenlignet med eksisterende standardbehandling til behandling af patienter med metastatisk kræft i mavesæk og mavemund (adenokarcinom), som tidligere er blevet behandlet med mindst to forudgående systemiske behandlingsregimer for fremskreden sygdom?

3.1 Kræft i mavesæk, mavemund og spiserør

Kræft i mavesæk (ventrikel), mavemund (gastroesophageal overgang) og spiserør (esophagus) hører samlet til den 8. hyppigste kræftform i Danmark [1]. Medianalderen for diagnosetidspunktet er for alle tre kræftformer omkring 70 år. En stor del af patienterne kan ikke tilbydes helbredende behandling, da de på diagnosetidspunktet enten har spredt sygdom eller er i for dårlig almen tilstand til at gennemgå behandling. Forekomsten af adenokarcinom i mavemund er steget i de senere år og er nu hyppigere end adenokarcinomer i den distale del af ventriklen. Risikofaktorer for udvikling af adenokarcinom i mavemunden omfatter reflukssygdom, Barrets øsofagus og overvægt. I Danmark behandles patientgruppen samlet via et multidisciplinært esofagus- og ventrikelcancerteam på fire afdelinger (Rigshospitalet, Odense Universitetshospital, Aalborg Universitetshospital og Aarhus Universitetshospital).

Symptomer på kræft i mavesæk eller mavemund kommer oftest snigende. De mest almindelige symptomer er kvalme, opkastning, synkebesvær, manglende appetit eller smerter i den øverste del af maven. Vægttabet kan være betydende og nødvendiggøre ernæringsterapi, før målrettet kræftbehandling kan komme på tale. Sygdommen kan medføre blodmangel, fordi der langsomt siver blod ud fra kræftknuden. I så fald er træthed et af de første tegn på sygdommen. Smerter er et hyppigt symptom, der ofte kræver smertestillende medicin.

I 2018 blev der i Danmark registreret 1.151 nye tilfælde af patienter med kræft i spiserør, mavesæk eller mavemund ifølge Dansk Esophagus Cardia Ventrikelkarcinom (DEGC)-databasen [1]. Af disse var der 633 tilfælde af adenokarcinom i mavemunden og 237 tilfælde af adenokarcinom i mavesækken, i alt 870 patienter. Ved diagnose har ca. 40 % metastatisk kræft, svarende til ca. 350 patienter [1]. Herudover er der en gruppe af patienter med lokaliseret eller lokal-avanceret sygdom, hvor tumor ikke kan reseceres (ikke-resektabel sygdom), eller hvor patienten grundet nedsat almen tilstand eller komorbiditet ikke er operabel eller tilgængelig for kurativt intenderet, onkologisk behandling. Fagudvalget skønner, at der årligt er ca. 600 patienter, hvor kræften er

inoperabel eller metastatisk, og hvor der potentielt er mulighed for pallierende, onkologisk behandling i form af kombinationskemoterapi [2]. En stor del af disse patienter er i så dårlig almentilstand eller med så betydende komorbiditet, at systemisk onkologisk behandling ikke kommer på tale [3]. Det skønnes, at ca. 300 patienter pr. år vil modtage 1. linje, systemisk behandling med kombinationskemoterapi. Af patienter behandlet med kemoterapi med palliativt sigte er 31 % i live 1 år efter start på første systemiske behandling, ganske få er i live efter 5 år [1].

3.2 Nuværende behandling

De kliniske retningslinjer er beskrevet af Danske Multidisciplinære Cancer Grupper (DMCG) [4]. Kemoterapi forlænger levetiden og bedrer livskvaliteten og tilbydes patienter i god almentilstand med inorperabel sygdom i mavesæk og mavemund. Fagudvalget anslår, at ca. 300 af de 600 årlige tilfælde af inoperabel eller metastatisk kræft i mavesæk og mavemund vil kunne tilbydes 1.-linje kemoterapi, mens den anden halvdel vil få tilbudt best supportive care (BSC, palliativ behandling, bestående af smerte- og symptomlindring, eventuelt på palliativ enhed eller hospice).
Kemoterapibehandlingen er en kombination af et platinholdigt kemoterapeutikum (cis- eller oxaliplatin) og en antimetabolit (5-Fluoropyrimidin (5-FU), capecitabine eller S1), evt. med tillæg af taxan. Ved avanceret kræft i mavesækken er kemoterapi forbundet med en median overlevelsesgevinst på ca. 7 måneder (fra 4 til ca. 11 måneder), sammenlignet med BSC [5]. Det er vist, at kombinationsbehandling er mere effektiv end enkeltstofbehandling [5]. Kombinationskemoterapi kan dog medføre betydende bivirkninger, se nedenfor. Patienten skal fremstå i en almentilstand, hvor det skønnes, at behandlingen ikke vil medføre livsforkortende eller livskvalitetsreducerende bivirkninger. Dette betyder typisk, at patienten fremstår i performancestatus (PS) 0-2 samt uden betydelig komorbiditet. Patienter i dårligere almentilstand (PS 3-4) eller betydelig komorbiditet anbefales BSC.

Af de ca. 300 behandlede patienter vil ca. halvdelen være i god almentilstand, når 1.linjebehandlingen ophører med at virke, og sygdommen forværres (progression). Disse patienter er kandidater til 2. linje kemoterapi. Baseret på mindre randomiserede ikke-registreringsstudier består behandlingen ofte af et taxan (paclitaxel, docetaxel) eller irinotecan. Disse lægemidler er ikke godkendt til behandling af kræft i mavesæk eller mavemund i 2. linje (off-label-anvendelse), men alle tre lægemidler har været omfattet af den tidligere anvendte danske indikation "visse maligne lidelser" og har været anvendt i Danmark i en årrække. Paclitaxel, docetaxel og irinotecan anses som ligeværdige behandlinger til 2. linjebehandling af kræft i mavesæk og mavemund. Den mediane overlevelse (OS) er i studier fundet til 5-6 måneder, dog i nyere randomiserede studier 7-8 måneder i den taxanbaserede kontrolarm [6–8]. Etårsoverlevelse efter start på 2.linjebehandling er i randomiserede studier mellem 20-30 % [6–12]. Af ovenstående årsager er 2. linje kemoterapi standard til patienter i god almen tilstand og med normalt eller let nedsat funktionsniveau [8–11,13].

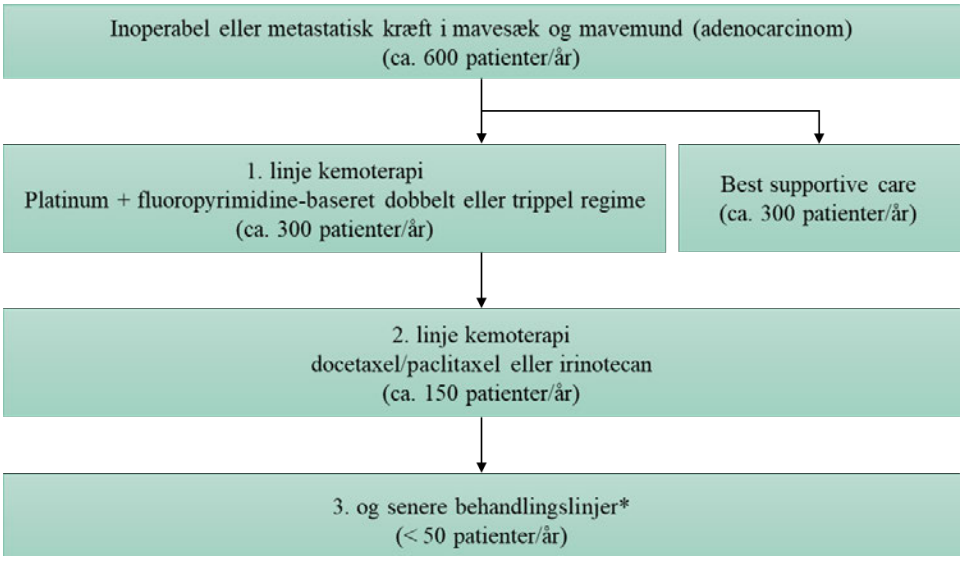
Den EMA-godkendte indikation for trifluridin/tipiracil er patienter, som har modtaget mindst to forudgående systemiske behandlingsregimer for fremskreden sygdom og er

kandidater til 3.linje systemisk behandling. Samlet anslår fagudvalget, at under 50 patienter årligt vil være kandidater til trifluridin/tipiracil.

Aktuelt findes ikke godkendte 3. linjebehandlinger med veldokumenteret effekt, og de fleste patienter overgår til palliativ behandling. Hos et fåtal af patienter kan der forsøges med systemisk, antineoplastisk behandling i 3. linje. Det sker ved sekventiel anvendelse af lægemidlerne fra 2. linje, dvs. disse kan anvendes, hvis de ikke tidligere har været anvendt. Det skal dog understreges, at dette ikke kan betragtes eller i praksis fungere, som standardbehandling, da der ikke findes dokumentation for effekten af taxaner eller irinotecan efter 2. linje.

En oversigt over anslåede årlige tilfælde pr. behandlingslinje fremgår af figur 1.

Figur 1. Oversigt over behandling for patienter med kræft i mavesæk og mavemund.



*patienter med performancestatus 0-1, som har mulighed for behandling i 3. linje.

Bivirkninger

Fagudvalget bemærker, at de typiske akutte bivirkninger til kemoterapi er træthed, der påvirker patienternes funktionsniveau. Kemoterapi medfører ofte kvalme, opkastninger, nedsat appetit, mundhulegener, mavesmerter eller diarré, hvilket yderligere øger risikoen for vægttab, som er et kardinalsymptom hos denne patientgruppe. Påvirkning af knoglemarven kan give nedsat immunforsvar, blodmangel og risiko for blødninger. Af mere kronisk karakter kan være risikoen for påvirkning af hørelse, nedsat nyrefunktion, nervebetændelse samt påvirkning af hjerte- og lungefunktion.

3.3 Trifluridin/tipiracil

Trifluridin/tipiracil består af en antineoplastisk thymidinbaseret nukleosidanalog; trifluridin og en thymidinphosphorylase (TPase)-hæmmer. Efter optagelse i kræftcellerne fosforyleres trifluridin af thymidinkinase og metaboliseres yderligere til et deoxyribonukleinsyre (DNA)-substrat. Det inkorporeres derefter direkte i DNA og interfererer derved med DNA-funktionen for at forhindre celleproliferation. Trifluridin

nedbrydes imidlertid hurtigt af TPase og metaboliseres let ved en første-passage-effekt efter oral indgivelse, hvorfor det gives i kombination (i samme tablet) med TPase-hæmmeren tipiracil.

Trifluridin/tipiracil doseres med 35 mg/m^2/dosis administreret oralt to gange dagligt på dag 1 til 5 og dag 8 til 12 i hver 28-dages cyklus, så længe der observeres behandlingsmæssige fordele eller indtil uacceptabel toksicitet. Dosis beregnes ud fra kroppens overfladeareal.

Denne vurdering omhandler trifluridin/tipiracil med den EMA-godkendte indikation: *Monoterapi til behandling af metastatisk kræft i mavesæk og mavemund (adenokarcinom) hos voksne patienter, som tidligere er blevet behandlet med mindst to forudgående systemiske behandlingsregimer for fremskreden sygdom.*

Trifluridin/tipiracil er også indiceret som monoterapi til behandling af voksne patienter med metastatisk kolorektalkræft (CRC), som tidligere er blevet behandlet med eller ikke betragtes som kandidater til tilgængelige terapier, herunder fluoropyrimidin-, oxaliplatin- og irinotecan-baserede kemoterapier, anti-VEGF-midler og anti-EGFR-midler.

4. Metode

Medicinrådets protokol for vurdering vedrørende trifluridin/tipiracil (Lonsurf®) som monoterapi til behandling af patienter med metastatisk kræft i mavesæk og mavemund (adenokarcinom) efter mindst to tidligere systemiske behandlinger for fremskreden sygdom beskriver sammen med Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser, hvordan Medicinrådet vil vurdere lægemidlets værdi for patienterne.

5. Resultater

5.1 Klinisk spørgsmål 1

5.1.1 Litteratur

Nedenfor beskriver og vurderer Medicinrådet den litteratur, som ansøger har anvendt i sin endelige ansøgning. Ansøgningen baserer sig i overensstemmelse med protokollen på det kliniske forsøg (TAGS).

TAGS er et klinisk randomiseret, placebo-kontrolleret forsøg som havde til formål at evaluere effekt og sikkerhed ved behandling med trifluridin/tipiracil, sammenlignet med placebo, til tidligere behandlede patienter med metastatisk mavekræft. Alle patienter blev behandlet med *best supportive care* (BSC) i tillæg til henholdsvis trifluridin/tipiracil og placebo. Der er ikke en standard godkendt behandling til 3. linje, og BSC er normalt

fokuseret på symptomlindring. Data blev indsamlet på 110 lokationer fordelt på 17 lande i perioden februar 2016 til januar 2018.

Resultater fra TAGS er rapporteret i tre publikationer, som er angivet i tabel 1.

Tabel 1. Oversigt over publikationer og kliniske forsøg

Publikationer	Klinisk forsøg	NCT-nummer	Median opfølgningstid
Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. Shitara K et al. The Lancet Oncology. 2018;19(11):1437-48.	TAGS (TAS-102 Gastric Study)	NCT02500043	10,7 måneder
Health-related quality of life associated with trifluridine/tipiracil in heavily pretreated metastatic gastric cancer: results from TAGS. Tabernero et al. Gastric Cancer. 2020;23: 689–698.			Data cut-off efter henholdsvis 6 og 3 serier a 28 dage for trifluridine tipiracil- og placebo-grupperne
Trifluridine/tipiracil versus placebo for third or later lines of treatment in metastatic gastric cancer: an exploratory subgroup analysis from the TAGS study. Tabernero et al. ESMO open. 2021 Aug 1;6(4):100200.			Post-hoc subgruppeanalyse, 10,7 måneder

Populationen i TAGS var patienter, som havde histologisk bekræftet ikke-resektabel, metastatisk adenokarcinom i mavesæk eller mavemund, og tidligere havde fået mindst to behandlingsregimer indeholdende fluoropyrimidin, platin og enten taxan og/eller irinotecan.

Baselinekarakteristika for patientpopulationen fremgår af tabel 2. Af EMAs EPAR fremgår det, at 63 % og 62 % i henholdsvis trifluridin/tipiracil og placebo-grupperne tidligere har fået tre eller flere systemiske behandlinger. Dermed har knapt 40 % af patienterne fået to tidligere behandlinger, som det fremgår af tabel 2.

De tidligere behandlinger inkluderede blandt andet ramucirumab (34% i trifluridin/tipiracil-arm og 32% i placebo), men det er ikke et muligt behandlingsalternativ i dansk praksis. Patienterne i studiepopulationen i performance status 0-1, hvilket også gælder de patienter, der er i en dansk kontekst potentielt, vil blive tilbudt behandlingen med trifluridin/tipiracil.

Fagudvalget vurderer, at populationen i TAGS overordnet set er tilsvarende de danske patienter, som vil være kandidater til trifluridin/tipiracil, hvad angår køn, alder, performance status og patologi. Dog adskiller den danske patientpopulation sig fra TAGS studiet ved, at hovedparten typisk kun har fået to behandlinger tidligere. Fagudvalget vurderer, at det har betydning for overførbarheden af resultaterne til den danske patientpopulation, som må forventes at have en lidt bedre prognose.

Tabel 2. Baselinekarakteristika

	Trifluridin/tipiracil (n = 337)	Placebo (n = 170)
Alder, median (IQR)	64 år (56-70)	63 år (56-69)
Køn, mænd (%)	252 (75)	117 (69)
Etnicitet (%)		
Kaukasisk	244 (72)	113 (66)
Asiatisk	51 (15)	29 (17)
Andet	4 (1)	4 (2)
Ikke oplyst	38 (11)	24 (14)
Region (%)		
USA	21 (6)	5 (3)
Europa	270 (80)	138 (81)
Japan	46 (14)	27 (16)
ECOG performance status (%)		
0	123 (36)	68 (40)
1	214 (64)	102 (60)
Primær tumorlokation (%)		
Mave	239 (71)	121 (71)
Mavemund	98 (29)	47 (28)
Begge	0	2 (1)
Målbar sygdom (%)	306 (91)	150 (88)
Histologi (%)		
Diffus	53 (16)	21 (12)
Intestinal	103 (31)	52 (31)
Blandet	14 (4)	8 (5)
Ukendt	132 (39)	69 (41)
Ikke oplyst	35 (10)	20 (12)
HER2 status (%)		
Positive	67 (20)	27 (16)
Negative	207 (61)	106 (62)
Ikke oplyst	63 (19)	37 (22)
Antal metastaselokationer		
1-2	155 (46)	72 (42)
≥ 3	182 (54)	98 (58)
Metastaser i bughinden (%)	87 (26)	53 (31)
Tidligere hel el. delvis fjernelse af mavesækken (%)	147 (44)	74 (44)
Antal tidligere kemoterapier (%)		
2	126 (37)	64 (38)
3	134 (40)	60 (35)
>4	77 (73)	46 (27)

	Trifluridin/tipiracil (n = 337)	Placebo (n = 170)
Tidligere kemoterapier (%)		
Platin	337 (100)	170 (100)
Fluoropyrimidin	336 (>99)	170 (100)
Taxan*	311 (92)	148 (87)
Irinotecan*	183 (54)	98 (58)
Ramucirumab	114 (34)	55 (32)
Anti-HER2 terapi	60 (18)	24 (14)
Immunterapi (anti-PD-1, anti-PD-L1)	25 (7)	7 (4)
Øvrige	77 (23)	41 (24)

IQR: interquartile range
*alle patienter havde fået taxan, irinotecan eller begge dele.

5.1.2 Databehandling og analyse

I dette afsnit er ansøgers datagrundlag, databehandling og analyse for hvert effektmål beskrevet.

Samlet overlevelse
Ansøger har indsendt estimater for medianoverlevelse samt andel, der fortsat er i live efter 6 måneder, jf. protokollen.

Usikkerheden ved Kaplan-Meier-kurverne er lille, da overlevelsesdata er modne, baseret på at 72,4 % og 82,4 % er døde i henholdsvis trifluridin/tipiracil- og placebo-gruppen.

Ansøger har indsendt en eksplorativ post-hoc subgruppeanalyse for den gruppe patienter, der tidligere har gennemgået to systemiske behandlinger fra et abstract [14]. Studiet er siden blevet publiceret [15]. Denne finder fagudvalget relevant at inddrage som supplerende oplysning i vurderingen, da det formodes at afspejle størstedelen af de patienter, som potentielt vil blive tilbudt trifluridin/tipiracil i dansk praksis.

I tillæg har ansøger indsendt data efter 12 måneder fra TAGS studiet [8], og fagudvalget har valgt at inddrage disse data fra det senere opfølgningstidspunkt.

Uønskede hændelser
I TAGS-studiet blev uønskede hændelser registreret og klassificeret efter gældende standarder for kliniske forsøg med kræftlægemidler for patienter, som modtog behandling (trifluridin/tipiracil: 335 ud af 337, placebo: 168 ud af 170).

Ansøger har ikke udregnet den relative effektforskel for den andel, der oplever uønskede hændelser grad 3-5. Derfor har Medicinrådet udregnet disse effektforskelle, baseret på data ekstraheret fra TAGS-studiet.

Livskvalitet
I protokollen blev defineret følgende måleenheder for livskvalitet: EORTC-QOL-C30 og EORTC-QOL-STO22 (mindste klinisk relevante forskel på 10 point) og median tid til forværring i performance status, defineret som PS $\geq$ 2 (mindste klinisk relevante forskel på 3 måneder).

Ansøger har indsendt data for median tid til forværring i performance status, jf. protokollen. For EORTC-QOL-C30 er der ligeledes indsendt data for tid til forværring

(defineret som forskel på mindst 5 point). For EORTC-QOL-STO22 er der ikke indsendt data for effektforskel.

Fagudvalget vurderer, at disse data kan anvendes i vurderingen. Som mindste klinisk relevante forskel anvendes de 3 måneder, der blev defineret for median tid til forværring i performance status.

Progressionsfri overlevelse (PFS)
Ansøger har indsendt estimater for median PFS samt andel, der fortsat er uden progression efter 6 måneder, jf. protokollen.

Ansøger har indsendt en post-hoc eksplorativ subgruppeanalyse for patienter, der tidligere har fået to systemiske behandlinger fra et abstract [14]. Studiet er siden blevet publiceret [15]. Denne finder fagudvalget relevant at inddrage som supplerende oplysning i vurderingen.

5.1.3 Evidensens kvalitet

Medicinrådet har anvendt GRADE til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Nedenfor følger en beskrivelse af vurderingen af de væsentligste domæner for hvert klinisk spørgsmål. Den fuldstændige GRADE-vurdering og begrundelserne er samlet i en GRADE-profil (bilag 2).

Evidensens kvalitet er lav, hvilket betyder, at nye studier med moderat eller høj sandsynlighed kan ændre konklusionen.

Medicinrådet har vurderet studierne ved Cochrane risk of bias tool 2.0. Overordnet er det vurderet, at risikoen for bias er lav for alle effektmål med undtagelse af livskvalitet (forbehold). I evalueringen af livskvalitet er der forskel på, hvor stor en andel EORTC-QOL-C30 data der er tilgængeligt for interventionsarmen sammenlignet med placebo med op til 22 %.Vurdering af risikoen for bias ved de enkelte studier (TAGS) og fra to artikler Shitara et al 2018 [8] og Tabernero et al 2020 [16] fremgår af bilag 1.

5.1.4 Effektestimater og kategorier

I tabellen herunder fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 1.

Tabel 3. Resultater for klinisk spørgsmål 1

Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel [95 % CI]	Foreløbig værdi	Forskel [95 % CI]	Foreløbig værdi	
Samlet overlevelse (OS)	Medianoverlevelse (3 måneder)	Kritisk	2,1 måneder	Kan ikke kategoriseres	HR 0,69 [0,56; 0,85]	Moderat merværdi	Lille merværdi
	Andel der fortsat er i live efter 6 måneder (5 %-point)		14 %-point	Kan ikke kategoriseres			
Uønskede hændelser	Andel af patienter der oplever grad 3-5 uønskede hændelser (10 %-point)	Kritisk	22 %-point*	Kan ikke kategoriseres	RR 1,39 [1,21; 1,60]*	Negativ værdi	Negativ værdi
	Kvalitativ gennemgang af rapporterede bivirkninger og uønskede hændelser		Se tekst				
Livskvalitet	Median tid til forværring i EORTC-QOL-C30 (5-point)	Vigtigt	0,3 måneder	Kan ikke kategoriseres	HR 1,27 [0,85; 1,87]	Kan ikke kategoriseres	Ingen dokumenteret merværdi
	Median tid til forværring i EORTC-QOL-STO22 (3 måneder)		*Ikke beregnet af ansøger*				
	Median tid til forværring i performance status (PS ≥ 2) (3 måneder)		2 måneder	Kan ikke kategoriseres	HR 0,69 [0,56; 0,85]	Moderat merværdi	
Progressionsfri overlevelse (PFS)	Median PFS (3 måneder)	Vigtigt	0,2 måned	Kan ikke kategoriseres	HR 0,57 [0,47; 0,70]	Stor merværdi	Lille merværdi
	Andel der fortsat er i PFS efter 6 måneder (5 %-point)		9 %-point	Kan ikke kategoriseres			
Konklusion							
Samlet kategori for lægemidlets værdi		Lille merværdi					
Kvalitet af den samlede evidens		Lav					

CI = konfidensinterval, HR = Hazard Ratio.

* Beregnet af Medicinrådet ud fra data fra TAGS-studiet.

Samlet overlevelse

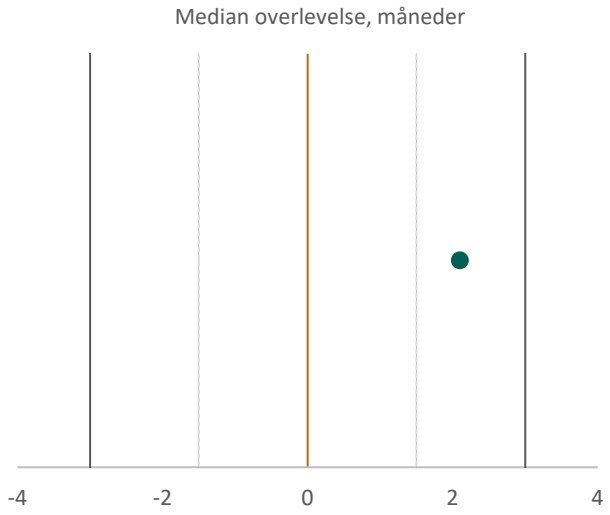
Som beskrevet i protokollen er effektmålet *Samlet overlevelse* kritisk for vurderingen af lægemidlets værdi for patienterne, fordi kræft i mavesæk og mavemund er en livstruende sygdom, og forbedret samlet overlevelse med mindst mulig toksicitet er det optimale mål for kræftbehandling.

Fagudvalget ønskede samlet overlevelse opgjort som medianoverlevelse samt overlevelsesrate efter 6 måneder.

Median overlevelse

Den mediane overlevelse i interventionsarmen var 5,7 måneder [95 % CI 4,8; 6,2], mens den i komparatorarmen var 3,6 måneder [95 % CI 3,1; 4,1]. Den absolutte forskel er dermed 2,1 måneder, hvilket ikke lever op til den prædefinerede mindste klinisk relevante effektforskel (MKRF), som det fremgår i figur 2. Den foreløbige værdi for den absolutte forskel kan ikke kategoriseres, da der ikke kan beregnes et konfidensinterval omkring forskellen.

I den post-hoc eksplorative subgruppeanalyse for patienter, der tidligere har fået to systemiske behandlinger, var den mediane overlevelse i interventionsarmen 6,8 måneder, mens den i komparatorarmen var 3,2 måneder. Den absolutte forskel er dermed 3,6 måneder (HR=0,67 [95 % CI 0,47;0.97], p=0,0318), hvilket afspejler en klinisk relevant effektforskel. Fagudvalget lægger vægt på subgruppeanalysen, da det er den subgruppe, der i dansk kontekst er kandidat til trifluridin/tipiracil behandlingen.



Figur 2. Punktestimat og 95 % konfidensinterval for den absolutte forskel for mediane overlevelse. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Overlevelsesrate ved 6 måneder

Efter 6 måneder var der fortsat 46,7 % [95 % CI 41,1; 52,2], der var i live i interventionsarmen, hvilket var tilfældet for 33,1 % [95 % CI 25,9; 40,3] i

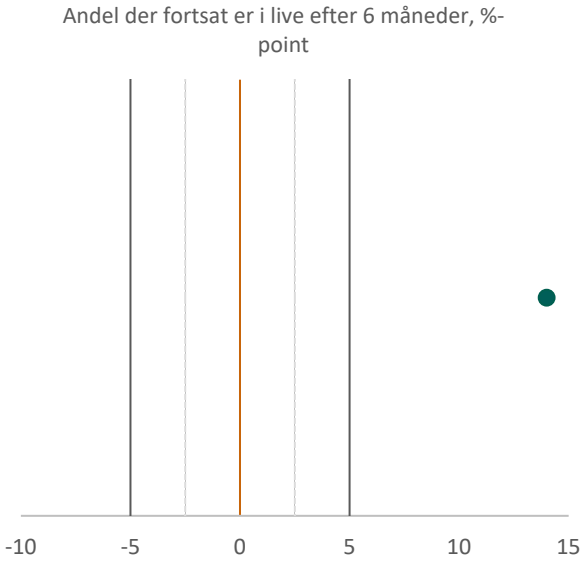
komparatorarmen. Punktestimatet for den absolutte forskel er dermed 14 %-point, hvilket afspejler en klinisk relevant effektforskel, som det fremgår i figur 3.

I en opdateret analyse var der efter 12 måneder fortsat 21,2 % og 13,0 % i live i henholdsvis interventions- og komparatorarmen.

Baseret på den relative effektforskel (HR 0,69 [0,56; 0,85]), som fremgår af tabel 3, har trifluridin/tipiracil foreløbigt en moderat merværdi vedr. overlevelse.

Samlet vurdering vedr. effektmålet overlevelse

Fagudvalget vurderer, at trifluridin/tipiracil aggregeret har en lille merværdi vedrørende samlet overlevelse. Trifluridin/tipiracil resulterer i median forøget overlevelse på 2,1 måneder, hvilket er mindre end MKRF, som er defineret til 3 måneder. Fagudvalget lægger i vurderingen dog vægt på den relative effektforskel, der giver en HR på 0,69 [95% CI 0,56; 0,85], og at der er 14 %-point flere, der fortsat er i live efter 6 måneder, som det fremgår af figur 3. Efter 12 måneder er der fortsat 8,2 %-point flere i live.



Figur 3. Punktestimat for den absolutte forskel for trifluridin/tipiracil i %-vis andel af patienterne, der fortsat er i live efter 6 måneder. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Uønskede hændelser

Som beskrevet i protokollen er effektmålet *uønskede hændelser* kritisk for vurderingen af lægemidlets værdi for patienterne, fordi uønskede hændelser ved behandling med kemoterapi ved kræft i mavesæk og mavemund kan være meget alvorlige og kan i nogle tilfælde medføre døden. Behandlingen er ikke kurativ, og det er derfor afgørende for valg af behandling, at patienterne ikke er påvirket af uønskede hændelser i deres resterende levetid.

Fagudvalget ønskede en fyldestgørende oversigt over uønskede hændelser med det formål at foretage en kvalitativ gennemgang af disse. Herunder en opgørelse af andel af patienter, der oplevede grad 3-5 uønskede hændelser.

Andel af patienter der oplevede grad 3-5 uønskede hændelser

I interventionsarmen var der 80 % (267/335), der oplevede grad 3-5 uønskede hændelser, hvilket var tilfældet i 58 % (97/168) i komparatorarmen. Den absolutte forskel er dermed 22 %-point, hvilket afspejler en klinisk relevant forskel.

Baseret på den relative effektforskel (RR 1,39 [1,21; 1,60]), som fremgår af tabel 3, har trifluridin/tipiracil foreløbigt en negativ værdi vedr. den andel, der oplever grad 3-5 uønskede hændelser.

Kvalitativ gennemgang af rapporterede uønskede hændelser

Tabel 4 viser en oversigt over uønskede hændelser rapporteret i TAGS.

Tabel 4. Uønskede hændelser rapporteret i TAGS

	Trifluridin/tipiracil (n=335)			**Placebo (n=168)**		
	Grad 3 Antal patienter (%)	**Grad 4** Antal patienter (%)	**Grad 5** Antal patienter (%)	**Grad 3** Antal patienter (%)	**Grad 4** Antal patienter (%)	**Grad 5** Antal patienter (%)
Alle uønskede hændelser uanset årsag	172 (51)	51 (15)	44 (13)	64 (38)	14 (8)	14 (8)
Alle uønskede hændelser relateret til behandlingen	136 (41)	39 (12)	1 (<1)†	21 (13)	0	1 (1)‡
Mest almindelige uønskede hændelser						
Svimmelhed	10 (3)	0	0	5 (3)	0	0
Anæmi eller nedsat hæmoglobinkoncentration	63 (19)	1 (<1)	0	12 (7)	1 (1)	0
Nedsat appetit	28 (8)	1 (<1)	0	9 (5)	2 (1)	0
Opkast	10 (3)	2 (1)	0	3 (2)	0	0
Diarré	8 (2)	1 (<1)	0	3 (2)	0	0
Udmattethed	23 (7)	0	0	10 (6)	0	0
Neutropeni eller nedsat antal neutrofile celler	85 (25)	29 (9)	0	0	0	0
Asteni (fysisk og psykisk træthed/kraftesløshed)	14 (4)	2 (1)	0	11 (7)	0	0
Trombocytopeni eller nedsat antal blodplader	7 (2)	4 (1)	0	0	0	0

Leukopeni eller nedsat antal hvide blodlegemer	28 (8)	3 (1)	0	0	0	0
Mavesmerter	14 (4)	0	0	15 (9)	0	0
Forstoppelse	3 (1)	1 (<1)	0	4 (2)	0	0
Rygsmerter	2 (1)	0	0	4 (2)	0	0
Øget ALP koncentration i blodet	9 (3)	0	0	5 (3)	0	0
Åndenød	6 (2)	0	0	4 (2)	2 (1)	0
Synkebesvær	6 (2)	1 (<1)	0	4 (2)	0	0
Væske i bughulen	12 (4)	0	0	10 (6)	0	1 (1)
Generel forværring af fysisk helbred	4 (1)	1 (<1)	17 (5)	3 (2)	1 (1)	11 (7)
Lavt niveau af sodium i blodet	4 (1)	0	0	7 (4)	0	0
Øget γ-glutamyltransferase koncentration	2 (1)	1 (<1)	0	4 (2)	1 (1)	0

Data er angivet som antal (%) og baseret på alle patienter, som modtog behandling. Uønskede hændelser blev defineret ud fra Common Terminology Criteria for Adverse Events.
ALP: alkaline phosphatase (enzym til nedbrydning af proteiner).
† Årsag: hjertestop. ‡ Årsag: toksisk leverbetændelse.

Trifluridin/tipiracil har en højere andel af uønskede hændelser sammenlignet med placebobehandling. De uønskede hændelser er primært hæmatologiske, som er velkendte og let kan behandles. Hændelserne kan dog føre til pausering/dosisreduktion af behandlingen og dermed have konsekvenser for patientens behandlingsforløb. En af de hæmatologiske hændelser er neutropeni. Da der ikke er tale om febril neutropeni, er det ikke bekymrende. Det kan dog betyde, at patienten skal i profylaktisk behandling med granolocytkoloni stimulerende vækstfaktor (G-CSF) ved næste behandling. I TAGS var der 16 %, der fik G-CSF.

Fagudvalget vurderer, at trifluridin/tipiracil aggregeret har en negativ værdi vedr. uønskede hændelser, fordi der er flere uønskede hændelser sammenlignet med komparator. Dette er dog forventeligt, da komparator er placebo.

Fagudvalget vurderer, at trifluridin/tipiracil generelt er en veltolereret behandling. En del af de rapporterede uønskede hændelser er symptomer relateret til grundsygdommen, og som derfor vil afhjælpes ved effektiv behandling. Derfor betragter fagudvalget ikke disse som uønskede hændelser, hvilket understreges af, at der ikke er en overhyppighed ift. placebo.

Livskvalitet

Som beskrevet i protokollen er effektmålet *livskvalitet* vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi påvirkning af livskvaliteten som følge af behandling og grundsygdom betyder meget for den enkelte patient. Den potentielle

negative effekt på livskvaliteten vil ofte være afgørende for valg af behandling, særligt i en population med kort restlevetid.

Fagudvalget ønskede livskvalitet opgjort som ændring fra baseline til 1 måned efter afsluttet behandling ved brug af to spørgeskemaer: EORTC-QOL-C30, der giver information om overordnet helbredsrelateret livskvalitet og EORTC-QOL-STO22, der omhandler livskvalitet relateret til symptomer og gener ved kræft i mavesækken. Desuden er den mediane tid til forværring i performancestatus (PS), defineret som PS ≥ 2 anvendt. Da PS er et udtryk for patientens funktionsniveau, og desuden er afgørende for, hvilken behandling der kan tilbydes, anser fagudvalget det for et vigtigt supplement til vurdering af livskvaliteten.

EORTC-QOL-C30

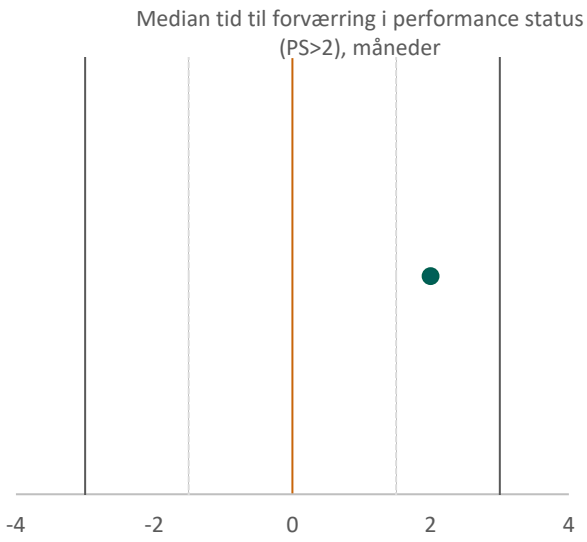
Som anført i afsnit 5.1.2 har ansøger indsendt data for tid til forværring i livskvalitet, defineret som ≥ 5 point på EORTC-QOL-C30. For interventionsgruppen var den mediane tid til forværring 2,6 måneder [95 % CI 2,3; 3,3] og for komparatorgruppen 2,3 måneder [95 % CI 1,4; ikke estimerbar], den absolutte effektforskel var 0,3 måneder. Baseret på den relative effektforskel (HR var 1,27 [0,85; 1,87]) var der ikke signifikant forskel i tid til forværring, men værdien kan ikke kategoriseres, fordi estimatet er for usikkert [16].

Median tid til forværring i performance status (PS ≥ 2)

For interventionsgruppen var den mediane tid til forværring 4,3 måneder [95 % CI 3,7; 4,7] og for komparatorgruppen 2,3 måneder [95 % CI 2,0; 2,8]. Den absolutte effektforskel var dermed 2 måneder, hvilket ikke afspejler en relevant forskel ifølge den nuværende grænse for MKRF, som er 3 måneder, hvilket fremgår af figur 3. Fagudvalget bemærker dog, at 2 måneder også er af stor betydning for denne type patienter med en dårlig prognose. Dette er understøttet af andre studier, hvor en udskydelse af progression, forværring af livskvalitet eller død på 2 måneder bliver afrapporteret som klinisk relevant [17–19].

Den relative effektforskel i PS (HR 0,69 [0,56; 0,85]), som fremgår af tabel 3, indikerer dog, at trifluridin/tipiracil har en moderat merværdi vedr. tid til forværring.

Fagudvalget vurderer, at trifluridin/tipiracil aggregeret ingen dokumenteret værdi har vedrørende livskvalitet.



Figur 3. Punktestimat for den absolutte forskel for trifluridin/tipiracil De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Progressionsfri overlevelse (PFS)

Som beskrevet i protokollen er effektmålet *Progressionsfri overlevelse* vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi det afspejler byrden af symptomer samt varigheden af den periode, hvor patienterne har det bedre, under 3.linjebehandling. PFS kan således give en anden information end overlevelse. Den tid der går uden sygdomsprogression vil typisk være præget af stabilitet eller bedring i symptomerne, herunder færre smerter og gener og bedre funktion, hvilket har stor indflydelse på patientens dagligdag og livskvalitet. PFS kan dermed anses som et surrogatmål for respons, men med inddragelse af tidsaspektet.

Fagudvalget ønskede PFS opgjort som median i antal måneder samt PFS-rate efter 6 måneder.

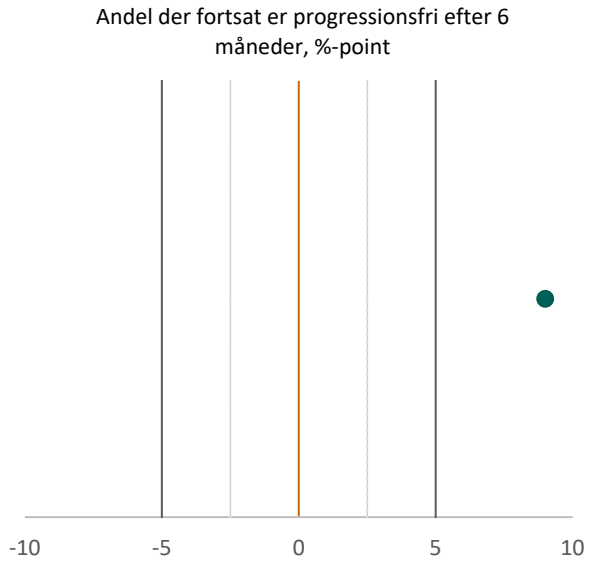
Den mediane PFS i interventionsarmen var 2 måneder [95 % CI 1,9; 2,3], mens den i komparatorarmen var 1,8 måneder [95 % CI 1,7; 1,9]. Den absolutte forskel er dermed 0,2 måneder, hvilket ikke afspejler en klinisk relevant effektforskel. I den eksplorative post-hoc subgruppeanalyse for patienter, der tidligere har fået to systemiske behandlinger, var den mediane PFS i interventionsarmen var 3,1 måneder, mens den i komparatorarmen var 1,9 måneder, hvilket ikke lever op til den prædefinerede MKRF (på 3 måneder), HR=0,54 [95 % CI 0,38;0,77), p=0,0004.

Efter 6 måneder var der fortsat 15 %, der var progressionsfri i interventionsarmen, hvilket var tilfældet for 6 % i komparatorarmen.

Baseret på den relative effektforskel (HR 0,57 [0,47; 0,70]), som fremgår af tabel 3, har trifluridin/tipiracil foreløbigt en stor merværdi vedr. PFS.

Fagudvalget vurderer, at trifluridin/tipiracil aggregeret har en lille merværdi for PFS. Vurderingen er baseret på, at den absolutte median gevinst for PFS med trifluridin/tipiracil behandlingen begrænser sig til 0,2 måneder og lever dermed ikke op til MKRF. Dog lægger FU i vurderingen vægt på, at der er 9 %-point flere, som fortsat er progressionsfri efter 6 måneder sammenlignet med placebo, som det fremgår af figur 4. Estimatet er dog usikkert, da det er baseret på få patienter.

Fagudvalget bemærker, at en subpopulation af trifluridin/tipiracil interventionsarmen har markant forbedret PFS sammenlignet med placebo. Desværre er det ikke muligt på forhånd at identificere, hvilke patienter der har udsigt til en markant forbedret PFS som følge af trifluridin/tipiracil behandlingen.



Figur 4. Punktestimat for den absolutte forskel for trifluridin/tipiracil. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

5.1.5 Fagudvalgets konklusion

Fagudvalget vurderer, at trifluridin/tipiracil som monoterapi til patienter med metastatisk kræft i mavesæk og mavemund (adenokarcinom) efter mindst to tidligere systemiske behandlinger for fremskreden sygdom samlet giver en lille merværdi sammenlignet med dansk standardbehandling, som er *best supportive care*.

Vurderingen er baseret på en direkte sammenligning i et randomiseret klinisk studie. Opfølgningstiden var lang nok til, at forskellen i median overlevelse og overlevelsesrater op til 6 og 12 måneder kunne vurderes.

I den samlede vurdering vægter fagudvalget effekten på det kritiske effektmål samlet overlevelse højt. Især effekten på andelen af overlevende efter henholdsvis 6 og 12 måneder med en forøgelse på hhv. 14 % og 8,2 %, da denne oversteg MKRF (5 %) samt den relative effektforskel, som indikerede en moderat merværdi. Den samlede median

overlevelse oversteg dog ikke MKRF på 3 måneder. Derfor vurderer fagudvalget, at trifluridin/tipiracil samlet har en lille merværdi for overlevelse.

Fagudvalget vurderer at trifluridin/tipiracil har lille merværdi for det kritiske effektmål PFS. I vurderingen lægges der vægt på, at 9 %-point flere patienter i behandlingsarmen fortsat er progressionsfri efter 6 måneder, men den mediane PFS lever ikke op til kriterierne for MKRF.

Fagudvalget vurderer, at trifluridin/tipiracil ingen dokumenteret merværdi har for livskvalitet, da tid til forværing i EORTC-QOL-C30 og PS ikke lever op til MKRF.

For det kritiske effektmål uønskede hændelser vurderer fagudvalget, at trifluridin/tipiracil aggregeret har en negativ værdi, fordi der er flere uønskede hændelser sammenlignet med komparator. Fagudvalget bemærker, at denne forskel er forventelig, da komparator er placebo. Generelt vurderer fagudvalget, at trifluridin/tipiracil ser ud til at være en veltolereret behandling, hvor patienternes livskvalitet ikke forværres under behandlingen, og tiden til funktionstab udsættes.

6. Andre overvejelser

Fagudvalget efterspurgte i protokollen, at ansøger belyser, hvorvidt der er en forskel på effekten afhængigt af, hvilken tidligere behandling patienten har fået (irinotecan eller taxan).

Ansøger beskriver, at der er udført subgruppeanalyser og multivariate analyser, som ikke kunne underbygge, at der er forskel i effekt afhængigt af tidligere behandling (irinotecan eller taxan).

Fagudvalget efterspurgte i protokollen, at ansøger indsendte opdaterede overlevelsesdata (baseret på et senere data cut-off i det identificerede studie), hvis det var muligt. Ansøger indsendte overlevelsesdata efter 12 måneder, men det var også publiceret i studie [8] og i EPAR.

7. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning fra Medicinrådet.

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9. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende kræft i mavesæk og mavemund	
Formand	**Indstillet af**
Lene Bæksgaard Jensen *Overlæge*	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Mette Karen Nytoft Yilmaz *Overlæge*	Region Nordjylland
Marianne Nordsmark *Overlæge*	Region Midtjylland
Helle Anita Jensen *Overlæge*	Region Syddanmark
Kenneth Hofland *Specialeansvarlig overlæge*	Region Sjælland
Jon Kroll Bjerregaard *Overlæge*	Region Hovedstaden
Natalia Marta Luczak *Farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Zandra Ennis *Afdelingslæge*	Dansk Selskab for Klinisk Farmakologi

Medicinrådets sekretariat
Medicinrådet
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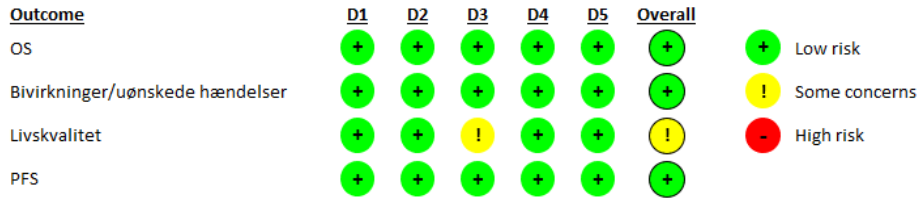
10. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	29.09.2021	Godkendt af Medicinrådet

11. Bilag

11.1 Bilag 1: Cochrane – risiko for bias

Tabel 5. Vurdering af risiko for bias ved Cochrane risk of bias tool 2.0. Shitara 2018 og Tabernero 2020, TAGS NCT02500043



D1 Risiko for bias i randomiserings-processen

D2 Effekt af tildeling til intervention

D3 Manglende data for effektmål

D4 Risiko for bias ved indsamlingen af data

D5 Risiko for bias ved udvælgelse af resultater, der rapporteres

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav for alle**	*"Patients were randomised (2:1) to trifluridine/tipiracil plus best supportive care or placebo plus best supportive care via a dynamic allocation method (biased coin) with an interactive-voice web-response system (IXRS). Almac (Craigavon, UK) operated the IXRS and created the algorithm that generated the individual patient allocation when the study site accessed the system"* Shitara et al.
Effekt af tildeling til intervention	**Lav for alle**	*"The IXRS randomly assigned study medication (trifluridine/tipiracil Or placebo) by assigning a kit number to that patient. Randomisation was stratified by region (Japan vs rest of world), ECOG performance status (0 vs 1), and previous treatment with ramucirumab (yes vs no). Patients, investigators and study-site personnel, those assessing outcomes, and those analysing the data were masked to treatment assignment."* Shitara et al.
Manglende data for effektmål	**Forbehold for Livskvalitet og lav for alle andre effektmål**	Data er afrapporteret for hovedparten af patienterne for alle effektmålene med undtagelse af EORTC.QOL-C30 hvor data foreligger for mellem 47.2-98% procent afhænigt af behandlingsgruppe og tidspunkt for evaluaering. Der er forske på hvor stor en andel EORTC-QOL-C30 data der er tilgængeligt for interventionsarmen sammenlignet med placebo med op til 22% difference.
Risiko for bias ved indsamlingen af data	**Lav for alle**	*"Patients, investigators and study-site personnel, those assessing outcomes, and those analysing the data were masked to treatment assignment"* Shitara et al.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav for alle**	Forud for studiet blev der lavet en plan for de de udførte statistiske analyser, denne er tilgængelig i det udgivne appendix og indeholder alle de nødvenige detaljer, sammen med protokollen. Alle effekmål fra protokollen og fra det kliniske studie var rapporteret.
Overordnet risiko for bias	**Forbehold for Livskvalitet og lav for alle andre effektmål**	Studiet er et randomiseret og dobbeltblændet phase III studiie. Data er indsamlet og analyseret efter en på forhånd angivet udførlig protokol og det vurderes således at den samlede risiko for bias er lav for alle andre effektmål end livskvalitet.

11.2 Bilag 2. GRADE

Tabel 6. GRADE evidensprofil for klinisk spørgsmål 1: trifluridin/tipiracil sammenlignet med placebo til behandling af <population>

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	trifluridin/tipiracil	placebo	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
Medianoverlevelse, 6 måneder												
1	RCT	Ikke alvorlig	Ikke alvorlig	Ikke alvorlig	Meget alvorlig[a]	Ingen	337	170	HR 0,69 [0,56; 0,85]	2,1 måneder	⊕⊕◯◯ LAV	KRITISK
Andel der fortsat er i live efter 6 måneder												
1	RCT	Ikke alvorlig	Ikke alvorlig	Ikke alvorlig	Alvorlig[b]	Ingen				13.6%	⊕⊕⊕◯ MODERAT	KRITISK
Bivirkninger, 3-5 uønskede hændelser												
1	RCT	Ikke alvorlig	Ikke alvorlig	Ikke alvorlig	Alvorlig[b]	Ingen	337	170	1,39 [1,21-1,60]	22% (12% - 34%)	⊕⊕⊕◯ MODERAT	KRITISK
Livskvalitet, Median tid til forværring i performance status (PS ≥ 2)												
1	RCT	Alvorlig[c]	Ikke alvorlig	Ikke alvorlig	Meget alvorlig[d]	Ingen	264	145	HR 0,69 [0,56; 0,85]	2 måneder	⊕◯◯◯ MEGET LAV	VIGTIG
Livskvalitet, median tid til forværring i EORTC-QOL-C30 ≥5 points												
1	RCT	Alvorlig[c]	Ikke alvorlig	Ikke alvorlig	Meget alvorlig[d]	Ingen	327	162	1,27 [0,85-1,87]	0,3 måneder	⊕◯◯◯ MEGET LAV	VIGTIG
Median Progressionsfri overlevelse, 6 måneder												

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	trifluridin/tipiracil	placebo	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
1	RCT	Ikke alvorlig	Ikke alvorlig	Ikke alvorlig	Meget alvorlig[a]	Ingen	337	170	HR 0,57 [0,47; 0,70]	0,2 måned	⊕⊕◯◯ LAV	VIGTIG
Andel der fortsat er uden progression efter 6 måneder												
1	RCT	Ikke alvorlig	Ikke alvorlig	Ikke alvorlig	Ikke alvorlig[b]	Ingen	337	170		9%	⊕⊕⊕◯ MODERAT	VIGTIG
Kvalitet af den samlede evidens			LAV[e]									

a Der er nedgraderet to niveauer, da der kun var ét studie og effekt var uner MKRF.
b Der er nedgraderet ét niveau, da der kun var ét studie.
c Der er nedgraderet to niveauer, da var nogle forbehold i vurderingen af risiko for biaskonfidensintervallet er meget bredt og indeholder både positive og negative konklusioner.
d Der er nedgraderet to niveauer, da der kun var ét studie og konfidensintervallet er meget bredt og indeholder både positive og negative konklusioner (under MKRF).
e Den samlede evidenskvalitet er vurderet ud fra den laveste kvalitet af de kritiske effektmål.

Application for the assessment of Lonsurf® (trifluridine/tipiracil) as monotherapy for the treatment of adult patients with metastatic gastric cancer, including adenocarcinoma of the gastro-oesophageal junction, after at least two previous treatments for advanced disease.

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Contents

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1. Basic information

Kontaktoplysninger	
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Overview of the pharmaceutical[6]	
Proprietary name	Lonsurf
Generic name	Trifluridine/tipiracil
Marketing authorization holder in Denmark	Servier A/S
ATC code	L01BC59
Pharmacotherapeutic group	Antineoplastic agents, antimetabolites
Active substance(s)	Trifluridine/tipiracil
Pharmaceutical form(s)	Tablet
Mechanism of action	Lonsurf is comprised of an antineoplastic thymidine-based nucleoside analogue, trifluridine, and the thymidine phosphorylase (TPase) inhibitor, tipiracil hydrochloride. Following uptake into cancer cells, trifluridine, is phosphorylated by thymidine kinase, further metabolised in cells to a deoxyribonucleic acid DNA substrate, and incorporated directly into DNA, thereby interfering with DNA function to prevent cell proliferation.

Overview of the pharmaceutical[6]	
Dosage regimen	-Method of administration: [redacted]. Tablets must be taken with a glass of water within 1 hour after completion of the morning and evening meals. -Posology: The [redacted] long as benefit is observed or until unnacceptable toxicity occurs. The [redacted]
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Lonsurf is indicated as monotherapy for the treatment of adult patients with metastatic gastric cancer including adenocarcinoma of the gastroesophageal junction, who have been previously treated with at least two prior systemic treatment regimens for advanced disease.
Other approved therapeutic indications	Lonsurf is indicated as monotherapy for the treatment of adult patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents.
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	No
Packaging – types, sizes/number of units, and concentrations	Pharmaceutical form: Lonsurf tablets, available in 2 strengths (15 mg trifluridine/6.14 mg tipiracil tablet and 20 mg trifluridine/8.19 mg tipiracil tablet). 20 and 60 tablets for each strength.
Orphan drug designation	No

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2. Abbrevations

Abbreviation / term	Definition
AE	Adverse event
ANC	Absolute neutrophil count
BSA	Body surface area
AT	As-treated (population)
BSC	Best supportive care
CI	Confidence interval
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGA	Esophageal gastric adenocarcinoma
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer QOL Questionnaire – Core
EQ5D	EuroQOL five dimensions questionnaire
GEJ	Gastro-oesophageal junction
HR	Hazard ratio
HRQoL	Health related quality of life
ITT	Intention-to-Treat
mGC	Metastatic gastric cancer
OS	Overall survival
PD	Progressive disease
PFS	Progression Free Survival
PH	Proportional hazards
PR	Partial response
PS	Performance status
QLQ	Quality of life questionnaire
QoL	Quality of life
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
ROW	Rest of world
SD	Stable disease
SE	Standard error
SmPC	Summary of Product Characteristics
TR	Tumour response

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3. Summary

In Denmark, adenocarcinoma of the stomach and esophagus (EGA) accounts for 870 new cases.[1]
Of patients with a known stage at diagnosis, approximately 35.0% are diagnosed in the metastatic disease stage.[2] Patients diagnosed with early-stage Gastric Cancer (GC) can undergo curative treatment by radical surgical resection.[2] Surgical resection of GC, specifically at early stages, is potentially curative; however, following resection, disease relapse still occurs in the majority of patients.[3] For patients with metastatic EGA, the treatment choice is palliative systemic chemotherapy which prolongs OS to around 9 to 11 months.[4]
For fit patients with inoperable locally advanced or metastatic disease, current clinical guidelines, such as those from the European Society of Medical Oncology (ESMO), recommend the use of doublet or triplet platinum/fluoropyrimidine combinations as first-line treatment in human epidermal growth-factor receptor 2 (HER-2)-negative patients, and trastuzumab with platinum and fluoropyrimidine-based chemotherapy for HER-2 positive patients.[3,5] Taxanes (docetaxel, paclitaxel), irinotecan or ramucirumab (alone or in combination with paclitaxel) are recommended as second-line treatment options for patients with performance status (PS) 0–1.[3,5]

Third-line therapeutic treatment options are fragmented, and no standard of care treatment exists.[1] There is also a lack of evidence on the effectiveness of treatments in the third line. Therefore, it is anticipated that there are no relevant active comparators for third-line mGC other than best supportive care (BSC).
Trifluridine/tipiracil (Lonsurf®) is an anti-tumor agent composed of trifluridine, a nucleoside that is incorporated into the DNA of actively dividing cells including tumor cells and tipiracil hydrochloride that inhibits the breakdown of trifluridine and maintains plasma levels of the active cytotoxic drug.
At the ESMO Gastro-intestinal congress in June 2018 and at ESMO 2018, data from the international randomized double-blind TAGS Phase III study were presented and published the same year.[2] The TAGS study investigated the efficacy of trifluridine/tipiracil versus placebo in patients with mEGA refractory to 2 prior standard treatments. Trifluridine/tipiracil provided a 31% reduction in the risk of death (median OS prolonged from 3.6 to 5.7 months). Therapy with trifluridine/tipiracil was well tolerated resulting in more hematological toxicity (neutropenia), but no extra grade 3-4 non-hematological toxicity compared to placebo. Thirteen percent of patients in the trifluridine/tipiracil arm discontinued due to an adverse event compared to 17% in the placebo group, and it was concluded that "trifluridine/tipiracil showed a predictable and manageable safety profile". Quality of life (QoL) was maintained in TAGS, and there was a trend towards trifluridine/tipiracil reducing the risk of QoL deterioration compared with placebo.[7]

The anticipated target population for trifluridine/tipiracil, in line with the patient population included in the TAGS trial, is for the treatment of adult patients with metastatic gastric adenocarcinoma, including GEJ adenocarcinoma, who have received at least two prior therapies for metastatic disease.

Trifluridine/tipiracil has been included and referred to in the latest Danish guidelines. Trifluridine/tipiracil has not yet been evaluated by the Danish authorities for this indication.[9]

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4. Literature search have not been requested by DMC.

The protocol will guide you in relation to the relevance of performing a literature search.

If a literature search is requested, the search strategy must be carried out as defined in the protocol. The identified literature must be screened and assessed to be relevant for answering the clinical questions (PICOs) described in the protocol. The applicant must provide a PRISMA flow diagram showing the number of references identified and the number of included and excluded references. A list of references excluded after full-text screening must be provided, as an appendix including the reasons for exclusion of each reference.

In addition, the applicant is required to consult EMA's relevant scientific discussion, both with regards to the new medicine and the comparator(s).

If EMA's European public assessment report (EPAR) is not available online at the time of submission, the applicant is encouraged to send the preliminary EPAR together with the application.

Databases and search strategy

- *Include the complete search strategy used to search each database.*
- *The search strategy must include (as a minimum):*
    - *which database(s) were searched (and, when relevant, the platforms used)*
    - *applied search strings (if relevant, including filters and limits)*
    - *time period covered*
    - *date of the search*
    - *number of references in the search result.*
- *The study selection must be depicted in a flow diagram, PRISMA, (either inserted below the search strategy or attached as a separate file).*

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4.1 Relevant study -TAGS[2,7]

Table 1 Relevant study included in the assessment.

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question <x>*
Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. Shitara K, Doi T, Dvorkin M, Mansoor W, Arkenau H-T, Prokharau A, et al. The Lancet Oncology. 2018;19(11):1437-48. TAGS (TAS-102 Gastric Study)[2]	TAGS (TAS-102 Gastric Study)	NCT02500043	FPI: February 24 2016. LPI: January 5 2018. April 30 2018. TAGS completed.	
Health-related quality of life associated with trifluridine/tipiracil in heavily pretreated metastatic gastric cancer: results from TAGS. Tabernero et al. Gastric Cancer. 2020;23: 689–698.[7]				

*when multiple clinical questions are defined in the protocol

4.2 Main characteristics of included studies

Trifluridine/tipiracil versus placebo in patients with heavily pre-treated mGC (TAGS): a randomised, double-blind, placebo-controlled, phase III trial.

[redacted] to evaluate the efficacy and safety of trifluridine/tipiracil versus placebo in patients with previously treated mGC.

All patients were aged 18 or older with histologically confirmed, non-resectable, metastatic gastric adenocarcinoma (including adenocarcinoma of the GEJ) who had [redacted] (and had experienced radiological disease progression) that contained [redacted]

Patients received either oral trifluridine/tipiracil 35 mg/m² twice daily plus BSC or placebo twice daily plus BSC on days 1–5 and days 8–12 of each 28-day treatment cycle.

The follow-up period was between February 2016 – January 2018.

In the absence of death confirmation or for patients alive as of the OS cut-off date, survival time was censored at the date of last study follow-up, or the cut-off date, whichever was earlier. The OS cut-off date used for the primary analysis was based on the date of the 384th death in the study (27th March 2018). QoL was evaluated at baseline and at each treatment cycle, using the EORTC QLQ-C30 and EORTC QLQ-STO22 questionnaires; results were considered valid for analysis only if ≥ 10% of patients completed the questionnaires. Key QoL outcomes were mean changes from baseline and time to deterioration in QoL.

Please see table A2 for additional information.

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5. Clinical question

5.1 What is the value of trifluridine / tipiracil compared to existing standard treatment for the treatment of patients with metastatic cancer of the stomach, including GEJ adenocarcinoma, which have previously been treated with at least two prior systemic treatment regimens for advanced disease?

5.1.1 Presentation of relevant studies

Third-line therapeutic treatment options are fragmented, and no standard of care treatment exists.[1]
The TAGS trial was a multinational, double-blind, parallel, randomised, phase III study which investigated the efficacy and safety of oral trifluridine/tipiracil 35 mg/m2 plus BSC versus placebo plus BSC in patients with mGC who received at least two prior regimens for advanced disease.

5.1.2 Results per study - TAGS

OVERALL SURVIVAL[2,6]

Since the OS data of the TAGS trial are mature [redacted] uncertainty about extrapolation is small.

In the TAGS trial, the primary endpoint of OS was met, with the risk of death statistically significantly lower by 31% in the FTP/TPI group compared to the placebo group (HR: 0.69; 95% CI: 0.56–0.85, one-sided p=0.0003, two-sided p=0.0006). [redacted]

For OS, results obtained for all stratification factors and most subgroups were consistent with those obtained for the ITT population. The Hazard ratios (HR) consistently favor the trifluridine/tipiracil group with only 2 exceptions noted of the 49 subgroups examined (patients who did not receive taxane; patients with well-differentiated tumors). Both subgroups comprised a small number of patients (48 and 46, respectively), each accounting for less than 10% of the population. In both cases, corresponding PFS results clearly favored the trifluridine/tipiracil group. Multivariate analysis did not identify prior taxane use as a prognostic or predictive factor; while histology subtype showed some prognostic value, it did not demonstrate any predictive effect.[8]
The corresponding Kaplan-Meier curves overlapped for the 2 groups and crossed at times, making the HR estimate unreliable. A supportive multivariate analysis was performed for prior treatment with taxane and irinotecan (yes or no), which did not identify prior taxane or irinotecan use as a prognostic or a predictive factor.[8]

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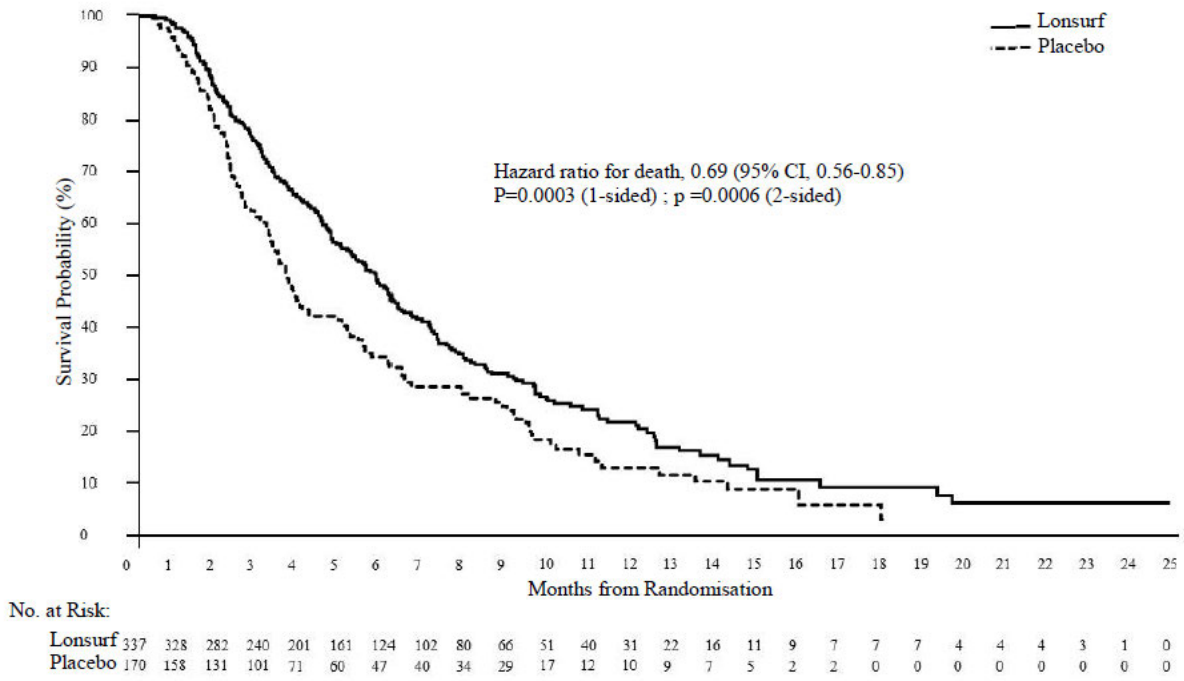
Figure 1. Kaplan-Meier curves of overall survival in TAGS[6]



[redacted]

Additionally, a new exploratory subgroup analysis has been conducted on the TAGS study, confirming the previous results and the therapeutic value of Lonsurf (Tabernero et al. 2021). The aim of the analysis was to separately assess the efficacy, safety and [redacted]

In this analysis, the median overall survival (mOS) was significantly longer in patients treated with FTD/TPI than with placebo in both the 3L group and the 4L+ group. When considering the overall population of the TAGS study the difference in OS was 2.1 months in favour of patients receiving FTD/TPI compared to those receiving BSC/placebo. With the updated analysis presented at ASCO GI 2021 the difference in the subgroup of patients treated with FTD/TPI compared to BSC/placebo in the 3rd line setting [redacted] The results are presented in Table 1.

Table 1. Results of the exploratory subgroup analysis of TAGS study

	FTD/TPI	BSC/Placebo	HR	CI 95%	P-value
3L patients					
OS	6.8	3.2	0.67	0.47–0.97	0.0318
PFS	3.1	1.9	0.54	0.38–0.77	0.0004
4L+ patients					
OS	5.2	3.7	0.72	0.55–0.95	0.0192
PFS	1.9	1.8	0.57	0.44–0.74	< 0.0001
Overall population					
OS	5.7	3.6	0.69	0.56–0.85	0.0006
PFS	2.0	1.8	0.57	0.47–0.70	< 0.0001

Source: (Tabernero et al. 2021)

Abbreviations: FTD/TPI= trifluridine/tipiracil, HR=Hazard ratio, CI=Confidence interval, OS=Overall survival, PFS=Progression-free survival, 3L= third-line setting, 4L+ = fourth/later-line setting.

[redacted] were no clinically significant deteriorations by ≥5 points in the mean QLQ-C30 total score or any subscale scores in either arm of the 3L group or the 4L+ group.

This subgroup analysis confirms the previously reported results and strengthens the scientific evidence of Lonsurf in the treatment of mGC, with a larger survival benefit in 3L which is the most common therapeutic setting of patients suffering from mGC and susceptible to be treated by Lonsurf in Finland. Results of quality of life in both 3L and 4L+ were consistent with previously published subgroup analyses and with the overall TAGS study population.

SAFETY[2.6]

Adverse event (AE) verbatim terms were coded and classified by system organ class and preferred term according to the MedDRA (version 20.1) terminology and the severity of the toxicities were graded according to the NCI CTCAE criteria, version 4.03, if applicable. AE incidence was calculated by the worst CTCAE grade at every level of summarization.

Trifluridine/tipiracil demonstrated a predictable and manageable safety profile, consistent with prior data. Safety was assessed in the TAGS trial among the population, which included the 503 patients who received treatment (trifluridine/tipiracil group n=335; placebo group n=168).

The overall incidence of adverse events was 97.3% for the trifluridin/tipiracil group and 93.5% for the placebo treatment group. A summary of the AE (including grade 1–2 events that were reported in 10% or more of patients and grade 3–5 events that were reported in 2% or more of patients).

The incidence of treatment-related adverse events was higher in the TAS-102 group than in the placebo group (80.9% and 56.6%, respectively), [redacted] treatment-related serious adverse events (11.6% and 3.6%, respectively). Serious adverse events and adverse events leading to death were comparable between treatment groups. The TAS-102 group had a lower incidence than the placebo group of adverse events leading to treatment discontinuation (12.8% and 16.7%, respectively. Hematologic impairment-related adverse events of special interest were experienced by 71.3% of patients in the TAS-102 group and 24.4% in the placebo group. Gastrointestinal-related adverse events (diarrhea and/or nausea and/or vomiting) were reported for 54.9% of patients in the TAS-102 group and 45.8% in the placebo group.

AE occurring at ≥ 10% higher incidence in the trifluridine/tipiracil group than in the placebo group were anemia, neutropenia, leukopenia, and neutrophil count decreased, which are established AE associated with the use of trifluridine/tipiracil.

Table 2: Total adverse events with Lonsurf

Total adverse events and adverse events for which grade 1–2 events were reported in 10% or more, or grade 3–5 were reported in 2% of patients in either treatment group

	Trifluridine/tipiracil group(n=335)				Placebo group (n=168)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any AE of any cause*	59 (18%)	172 (51%)	51 (15%)	44 (13%)	60 (36%)	64 (38%)	14 (8%)	19 (11%)
Any treatment-related AE	95 (28%)	136 (41%)	39 (12%)	1 (<1%)†	73 (43%)	21 (13%)	0	1 (1%)‡
Most common adverse events of any causes								
Nausea	114 (34%)	10 (3%)	0	0	48 (29%)	5 (3%)	0	0
Anaemia	86 (26%)	63 (19%)	1 (<1%)	0	19 (11%)	12 (7%)	1 (1%)	0
Decreased appetite	86 (26%)	28 (8%)	1 (<1%)	0	41 (24%)	9 (5%)	2 (1%)	0
Vomiting	71 (21%)	10 (3%)	2 (1%)	0	31 (18%)	3 (2%)	0	0
Diarrhoea	67 (20%)	8 (2%)	1 (<1%)	0	21 (13%)	3 (2%)	0	0
Fatigue	66 (20%)	23 (7%)	0	0	25 (15%)	10 (6%)	0	0
Neutropenia	62 (19%)	85 (25%)	29 (9%)	0	7 (4%)	0	0	0
Asthenia	49 (15%)	14 (4%)	2 (1%)	0	29 (17%)	11 (7%)	0	0
Thrombocytopenia	49 (15%)	7 (2%)	4 (1%)	0	8 (5%)	0	0	0
Leukopenia	47 (14%)	28 (8%)	3 (1%)	0	3 (2%)	0	0	0
Abdominal Pain	41 (12%)	14 (4%)	0	0	16 (10%)	15 (9%)	0	0
Constipation	41 (12%)	3 (1%)	1 (<1%)	0	16 (10%)	4 (2%)	0	0
Back Pain	23 (7%)	2 (1%)	0	0	7 (4%)	4 (2%)	0	0
↑ blood [alkaline phosphatase]	21 (6%)	9 (3%)	0	0	9 (5%)	5 (3%)	0	0
Dyspnoea	18 (5%)	6 (2%)	0	0	11 (7%)	4 (2%)	2 (1%)	0
Dysphagia	13 (4%)	6 (2%)	1 (<1%)	0	4 (2%)	4 (2%)	0	0
Ascites	7 (2%)	12 (4%)	0	0	5 (3%)	10 (6%)	0	1 (1%)
General deterioration of physical health	1 (<1%)	4 (1%)	1 (<1%)	17 (5%)	2 (1%)	3 (2%)	1 (1%)	11 (7%)
Hyponatraemia	1 (<1%)	4 (1%)	0	0	1 (1%)	7 (4%)	0	0
↑ γ-[glutamyltransferase]	1 (<1%)	2 (1%)	1 (<1%)	0	0	4 (2%)	1 (1%)	0

Note: Data are n (%) and are presented for all treated patients. Adverse events were defined according to the Common Terminology Criteria for Adverse Events; *Adverse event data were missing for accidental overdose (n=1 [<1%]) and drug misuse (n=1 [<1%]) in the trifluridine/tipiracil group and encephalopathy (n=1 [1%]) in the placebo group; †Attributed to cardiopulmonary arrest; ‡Attributed to toxic hepatitis.

Notification: No relative risk analysis versus placebo have been performed.

Table 3[11]: Adverse events leading to dosing modification or discontinuation of treatment*

	Trifluridine/tipiracil (n=335)†		Placebo (n=168)†	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Adverse events of any cause leading to dosing modification				
Any event	195 (58%)	148 (44%)	37 (22%)	29 (17%)
Most common events‡				
Neutropenia and/or decreased neutrophil count	123 (37%)	85 (25%)	1 (1%)	0
Anaemia and/or decreased haemoglobin level	29 (9%)	15 (4%)	3 (2%)	3 (2%)
Leucopenia and/or decreased white blood cell count	19 (6%)	11 (3%)	0	0
Treatment-related adverse events leading to discontinuation of treatment				
Any event	13 (4%)	13 (4%)	2 (1%)	2 (1%)
Thrombocytopenia	3 (1%)	3 (1%)	0	0
Diarrhoea	2 (1%)	1 (<1%)	1 (1%)	1 (1%)
Nausea	2 (1%)	2 (1%)	1 (1%)	1 (1%)
Neutropenic sepsis	2 (1%)	2 (1%)	0	0
Anaemia	1 (<1%)	1 (<1%)	0	0
Cerebrovascular accident	1 (<1%)	0	0	0
Decreased appetite	1 (<1%)	1 (<1%)	0	0
Fatigue	1 (<1%)	1 (<1%)	0	0
General physical health deterioration	1 (<1%)	1 (<1%)	0	0
Ileus	1 (<1%)	1 (<1%)	0	0
Neutropenia	1 (<1%)	1 (<1%)	0	0
Vomiting	0	0	2 (1%)	1 (1%)

Data are n (%).*Per Common Terminology Criteria for Adverse Events. †All treated patients. ‡Adverse events of any grade that occurred in 5% or more of patients in either treatment group.

QUALITY OF LIFE[7,8]

Of 507 randomized patients, 496 had baseline QoL data available. The analysis cut-off was 6 cycles for trifluridine/tipiracil and 3 cycles for placebo. In both treatment groups, there were no clinically significant deteriorations in the mean QLQ-C30 Global Health Status (GHS) score, or in most subscale scores. In a sensitivity analysis including death and disease progression as events, there was a trend towards trifluridine/tipiracil reducing the risk of deterioration of QoL scores compared with placebo. Deterioration in the GHS score was associated with deterioration in ECOG performance status (PS).

[redacted]

In the sensitivity analysis including death as an event, the risk of deterioration (by ≥ 10 points) in the QLQ-C30 GHS score was numerically lower with trifluridine/tipiracil than placebo (HR 0.92, 95% CI 0.74–1.16); similar findings were observed for all QLQ-C30 and QLQ-STO22 scores, with the exception of the physical functioning score. In this analysis, the median time to deterioration (by ≥ 10 points) in the QLQ-C30 GHS was 3.19 months (95% CI 2.80–3.82) for trifluridine/tipiracil and 2.27 months (95% CI 2.07–3.36) for placebo. In the second sensitivity analysis which included death or PD as an event, compared with placebo, trifluridine/tipiracil reduced the risk of deterioration (by ≥ 10 points) for all QLQ-C30 and QLQ-STO22 scores (HRs ranged from 0.55 to 0.75). For the QLQ-C30 GHS score, the median time to deterioration in this analysis was 2.11 months (95% CI 2.07–2.27) for trifluridine/tipiracil versus 1.88 months (95% CI 1.84–1.94) for placebo (HR 0.65, 95% CI 0.52–0.81).

QoL was maintained in TAGS, and there was a trend towards trifluridine/tipiracil reducing the risk of QoL deterioration compared with placebo.

Although there was slight deterioration from baseline during treatment in both groups, there were no clinically relevant changes (≥ 10 points) in the mean QLQ-C30 GHS scores or in most of the subscale scores at any time point for which there were sufficient data. With trifluridine/tipiracil, there were no clinically relevant deteriorations in any of the subscale scores from baseline until end of cycle 6, with the exception of deteriorations in the mean score of role functioning from baseline to the end of cycles 4 and 6 (−10.2 ± 24.2 and −13.4 ± 30.0, respectively).

In a sensitivity analysis that included death or progressive disease (PD) as an event, trifluridin/tipiracil prolonged time to deterioration in QoL versus placebo, where deterioration was a reduction of ≥10 points on the QLQ-C30 GHS score (Hazard ratio, HR=0.65; 95% CI, 0.52 to 0.81.

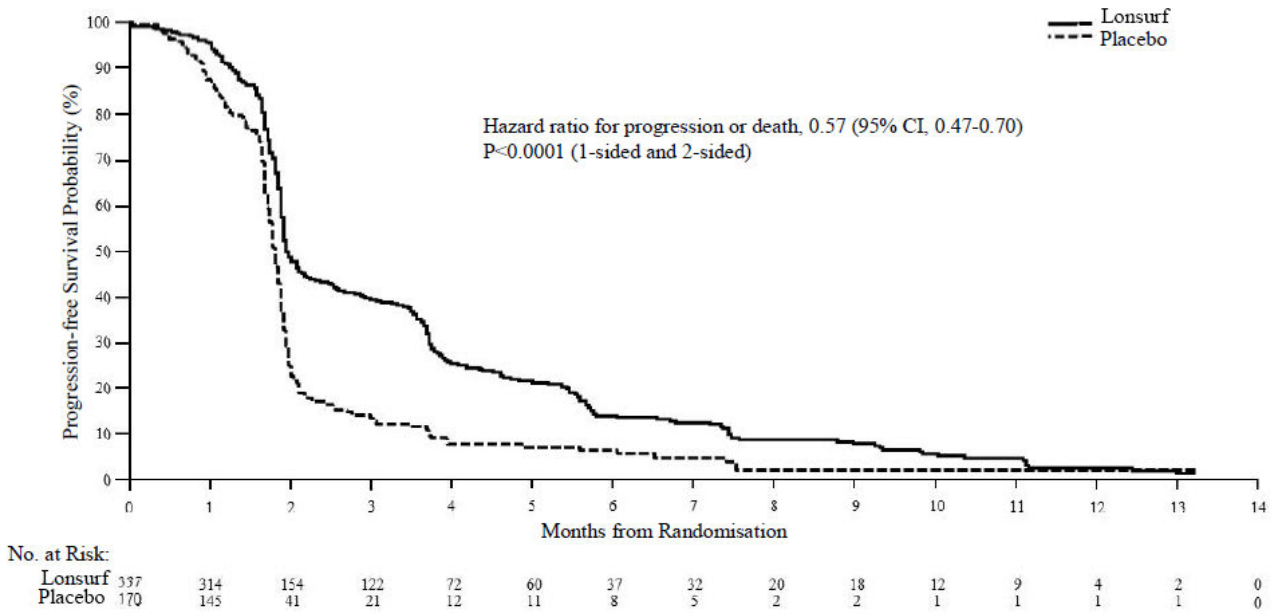
TIME TO ECOG PS DETERIORATION[2,6]

In the pre-specified analysis of time to worsening ECOG PS, patients in the trifluridine/tipiracil group experienced a longer period until ECOG PS score deterioration compared to placebo.

[redacted]

from the time of the initial tumor assessment.

Figure 2. Kaplan-Meier curves of progression free survival in TAGS[6]



5.1.3 Comparative analyses[2,6,7]

- [redacted]

- The overall incidence of adverse events was comparable between the 2 treatment groups. As expected, the incidence of treatment-related AEs was higher in the trifluridine/tipiracil group than in the placebo group, as well as Grade 3 or higher AE, and treatment-related serious AE. The incidence of AE of special interest was also higher in the FTP/TPI group than the placebo group. In the trifluridine/tipiracil group, AE reported for > 20% of patients were anemia, neutropenia, nausea, decreased appetite, fatigue, vomiting, and diarrhea. AE occurring at ≥ 10% higher incidence in the trifluridine/tipiracil group than in the placebo group were anemia, neutropenia, leukopenia, and neutrophil count decreased.

- Patients completed the EORTC QLQ-C30 and QLQ-STO22 questionnaires within 7 days prior to randomization, prior to dose administration on Day 1 of Cycles ≥ 2, and at the 30-day Safety Follow-up Visit if not performed within the prior 4 weeks. In this analysis, QoL was maintained in patients with heavily pretreated, mGC who received treatment with trifluridine/tipiracil, and there was a trend towards trifluridine/tipiracil reducing the risk of QoL deterioration compared with placebo.

- The key secondary endpoint of PFS showed a reduction in the risk of disease progression or death by 43% when directly compared to placebo, (1-sided and 2-sided $p < 0.0001$; stratified log-rank test), which translates into an over-tripling of PFS rates at 4 months (27% vs. 8%) and an over-doubling at 6 months (15% vs. 6%).

5.2 <Clinical question 2>. Not applicable

Not requested by the Danish Medicine Council.

5.2.1 Presentation of relevant studies. Not applicable

Not requested by the Danish Medicine Council.

5.2.2 Results per study. Not applicable

Not requested by the Danish Medicine Council.

5.2.3 Comparative analyses. Not applicable

Not requested by the Danish Medicine Council.

5.3 <Clinical question 3 ….>. Not applicable

Not requested by the Danish Medicine Council.

5.3.1 Presentation of relevant studies. Not applicable

Not requested by the Danish Medicine Council.

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5.3.2 Results per study. Not applicable

Not requested by the Danish Medicine Council.

5.3.3 Comparative analyses. Not applicable

Not requested by the Danish Medicine Council.

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7. Appendices

7.1 Literature search Not applicable, not requested by Danish Medicine Council

Table A1 Inclusion and exclusion criteria	
Inclusion criteria	Population: Intervention(s): Comparator(s): Outcomes: Settings (if applicable): Study design: Language restrictions: Other search limits or restrictions applied:
Exclusion criteria	Population: Intervention(s): Comparator(s): Outcomes: Settings (if applicable): Study design: Language restrictions: Other search limits or restrictions applied:

7.2 Main characteristics of included study

Table A2 Main study characteristics[2]	
Trial name	TAGS (TAS-102 Gastric Study)
NCT number	NCT02500043
Objective	Phase III, randomised, double-blind, placebo-controlled study at 110 sites in 18 countries to evaluate the efficacy and safety of trifluridine/tipiracil versus placebo in patients with previously treated metastatic gastric cancer (mGC).
Publications – title, author, journal, year	Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. Shitara K et al. The Lancet Oncology. 2018;19(11):1437-48. TAGS (TAS-102 Gastric Study).
Study type and design	Phase III, randomised, double-blind, placebo-controlled study at 110 sites in 18 countries to evaluate the efficacy and safety of trifluridine/tipiracil versus placebo in patients with previously treated mGC.

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Table A2 Main study characteristics[2]	
Follow-up time	February 2016 – January 2018 In the absence of death confirmation or for patients alive as of the OS cut-off date, survival time was censored at the date of last study follow-up, or the cut-off date, whichever was earlier. The OS cut-off date used for the primary analysis was based on the date of the 384th death in the study (27th March 2018).

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Population (inclusion and exclusion criteria)	**INCLUSION CRITERIA:** 1. Written informed consent 2. Histologically confirmed non-resectable, metastatic gastric adenocarcinoma (including adenocarcinoma of the GEJ) as defined by the AJCC staging classification. 3. Previously received at least two prior regimens (at least one cycle per regimen) for advanced disease and were refractory to or unable to tolerate their most recent prior therapy: a. Prior regimen(s) must have included a fluoropyrimidine, platinum, and either a taxane- and/or irinotecan-containing regimen; patients whose tumours were HER2+ must have received prior anti-HER2+ therapy if available. b. Patients had progressed based on imaging during or within three months of the last administration of their most recent prior regimen. c. Patients who had withdrawn from their most recent prior regimen due to unacceptable toxicity warranting discontinuation of treatment and precluding retreatment with the same agent prior to progression of disease were also eligible to enter the study. d. Patients who received postoperative adjuvant chemotherapy or chemo-radiotherapy and had recurrence during or within six months of completion of the adjuvant chemotherapy were allowed to count the adjuvant therapy as one prior regimen for advanced disease. Patients who received pre- and post-operative adjuvant chemotherapy and had recurrence during or within 6 months of completion of the adjuvant chemotherapy were allowed to count the adjuvant therapy as 1 prior regimen only if the same regimen was administered both pre- and post-operatively. 4. Had measurable or non-measurable disease as defined by RECIST 1.1 criteria. 5. Able to take medications orally (study treatment was not administered via a feeding tube). 6. Aged 18 years or older (20 years or older for patients in Japan). 7. ECOG PS of 0 or 1 at time of randomization. 8. Adequate organ function as defined by the following criteria: a. ANC of ≥ 1,500/mm3 (that is, ≥ 1.5 × 109/L by IU). b. Platelet count ≥ 100,000/mm3 (IU: ≥ 100 × 109/L). c. Haemoglobin value of ≥ 9.0 g/dL prior to randomisation based on measurements obtained 2 weeks or more after last transfusion received. d. AST and ALT ≤ 3.0 × ULN; if liver function abnormalities were due to underlying liver metastasis, AST and ALT ≤ 5 × ULN. e. Total serum bilirubin of ≤ 1.5 × ULN (except for Grade 1 hyperbilirubinemia due solely to a medical diagnosis of Gilbert's syndrome). f. Serum creatinine ≤ 1.5 mg/dL. 9. Was willing and able to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures. 10. Negative pregnancy test (urine or serum) within 7 days prior to starting the study drug. Both males and females agreed to use effective birth control during the study (prior to the first dose and for 6 months after the last dose) if conception was possible during this interval. **EXCLUSION CRITERIA:** 1. Had a serious illness or medical condition(s) including, but not limited to, the following: a. Concurrently active malignancies excluding malignancies that were disease-free for more than 5 years or carcinoma-in-situ deemed cured by adequate treatment. b. Known brain metastasis or leptomeningeal metastasis. c. Active infection (that is, body temperature ≥ 38°C due to infection) including active or unresolved pneumonia/pneumonitis. d. Intestinal obstruction, pulmonary fibrosis, renal failure, liver failure, or cerebrovascular disorder. e. Uncontrolled diabetes. f. Myocardial infarction within 12 months prior to randomisation, severe/unstable angina, symptomatic congestive heart failure New York Heart Association class III or IV. g. Gastrointestinal haemorrhage (Grade ≥ 3) within 2 weeks prior to randomization. h. Known HIV, AIDS-related illness, or chronic or acute hepatitis B or hepatitis C.

Table A2 Main study characteristics[2]	
	i. Patients with autoimmune disorders or history of organ transplantation who required immunosuppressive therapy. j. Psychiatric disease that may have increased the risk associated with study participation or study drug administration or may have interfered with the interpretation of study results. 2. Had any of the following within the specified time frame prior to randomization: a. Major surgery within prior 4 weeks. b. Any anticancer therapy within prior 3 weeks. c. Extended field radiation within prior 4 weeks or limited field radiation within prior 2 weeks. d. Any investigational drug/device received within prior 4 weeks. 3. Had previously received trifluridine/tipiracil. 4. Had unresolved toxicity of greater than or equal to CTCAE Grade 2 attributed to any prior therapies (excluding anaemia, alopecia, skin pigmentation, and platinum-induced neurotoxicity). 5. Was a pregnant or lactating female. 6. Was inappropriate for entry into this study in the judgment of the Investigator. 7. Had known or assumed hypersensitivity to trifluridine/tipiracil or any of its ingredients. *Insert the inclusion and exclusion criteria related to NCT number from www.clinicaltrials.gov*
Intervention	Trifluridine/tipiracil is administered orally at a dose of 35 mg/m² of body surface area (BSA) twice daily on days 1 to 5 and 8 to 12 of each 28-day treatment cycle. This dose was administered within the TAGS trial and is representative of the anticipated licensed dose for mGC. Treatment with trifluridine/tipiracil is continued until the first occurrence of any of the following: disease progression (determined within TAGS per the RECIST criteria), unacceptable levels of toxicity, withdrawal of consent or death. 507 patients were enrolled and randomly assigned, 337 to the trifluridine/tipiracil group and 170 to the placebo group.
Baseline characteristics	Demographic and baseline characteristics were summarized by treatment group using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) and/or frequency distributions, as appropriate. Specific characteristics and baseline strata are summarized in the publication. The treatment groups were generally comparable with respect to demographic characteristics. In the ITT population, the median age was 63.0 years (range: 24 to 89 years), with 45.0% ≥ 65 years and 13.6% ≥ 75 years. The racial composition of the ITT population was primarily White (70.4%) and Asian (15.8%). Per protocol, all patients had a baseline ECOG performance status of 0 (37.7%) or 1 (62.3%), although the trifluridine/tipiracil group had more patients with an ECOG performance status of 1 (63.5% vs 60.0% in the placebo group). Most patients (39.8%) had normal renal function or mild renal impairment (41.8%) at baseline. Median height (168.0 cm) and weight (65.8 kg) were also consistent between treatment groups. Most patients in the study were male (72.8%), with a higher proportion of male patients in the TAS-102 treatment group (74.8%) than in the placebo group (68.8%). Regional distribution of patients included 73 (14.4%) patients from Japan, 26 (5.1%) in the USA, and 408 (80.5%) in the EU. Median BSA for all patients was 1.740 m² and was lower for patients in Japan (1.650 m2) than patients in the USA (1.830 m2) and the EU (1.770 m²)

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Table A2 Main study characteristics[2]	
Primary and secondary endpoints	**Primary:** Overall survival (OS) **Key Secondary:** - Progression-free survival (PFS) based on Investigator assessment of radiologic images - Safety and tolerability **Other Secondary:** - Overall response rate (ORR) - Disease control rate (DCR) - Time to deterioration of Eastern Cooperative Oncology (ECOG) performance status to score of 2 or higher. - Quality of Life (QoL) as evaluated by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and the QLQ-STO22, which is a module specific to patients with gastric cancer State the primary and secondary outcomes of the study.
Method of analysis	This was a multinational, double-blind, 2-arm, parallel, randomized, Phase 3 study evaluating the efficacy and safety of trifluridine/tipiracil plus BSC versus placebo plus BSC in patients with metastatic gastric cancer who received at least 2 prior regimens for advanced disease. Eligible patients were centrally randomized (2:1) to trifluridine/tipiracil plus BSC (experimental arm) or placebo plus BSC (control arm). Randomization was stratified by: region (Japan vs ROW1 [European Union, United States]); ECOG performance status (0 vs 1); and prior treatment with ramucirumab (yes vs no). Computed tomography scans were performed at baseline and every 8 weeks thereafter until disease progression. On-site tumor assessments were performed by the Investigator/local radiologist using Response Evaluation Criteria in Solid Tumors (RECIST) (version 1.1, 2009). Patients who discontinued for reasons other than radiologic disease progression (ie, intolerable side effects), were followed every 8 weeks for tumor response until radiologic disease progression or initiation of new anticancer therapy (whichever occurred first). Quality of Life was evaluated using the EORTC QLQ-C30 and the QLQ-STO22 questionnaires. Safety assessments included recording of adverse events from the first dose of study treatment (or worsened after the start of treatment) through 30 days after the last dose of study treatment and graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Safety assessments also included evaluation of laboratory test results, vital signs measurements, physical examination findings, and changes in ECOG performance status score. The study was designed to detect with 90% power a hazard ratio (HR) for death of 0.70 (30% risk reduction) in the trifluridine/tipiracil group compared with the placebo group with an overall 1-sided type 1 error of 0.025. A variable accrual period of 18 months and a 5%/year loss to survival follow-up rate was assumed. Using a treatment allocation of 2:1 (trifluridine/tipiracil: placebo) of 500 patients, 384 deaths were targeted for the final OS analysis.
Subgroup analyses	A forest plot of the HRs for treatment effect on overall survival (OS) for predefined subgroups in the ITT population was carried out.

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7.3 Results per study

Table A3a Results of study TAGS											
Trial name:	TAGS (TAS-102 Gastric Study)										
NCT number:	NCT02500043										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
median overall survival	Trifluridine/ tipiracil	337	5.7 (4.8–6.2) months	2.1	NA	NA	HR: 0.69	0.56–0.85	0.0003	The median survival is based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm.	2.
	Placebo+BSC	170	3.6 (3.1–4.1) months								
6-month overall survival	Trifluridine/ tipiracil	337	46.7% [41.1, 52.2]	14%	NA	NA	NA	NA	NA	The median survival is based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm.	2.
	Placebo+BSC	170	33.1% [25.9, 40.3]								

Table A3a Results of study TAGS											
PFS	Trifluridine/ tipiracil	337	2.0 (1.9, 2.3)	0.2	NA	0.05	HR: 0.57	0.47-0.70	<0.0001	The median survival is based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm.	2.
	Placebo+BSC	170	1.8 (1.7, 1.9)								
6 month PFS	Trifluridine/ tipiracil	337	15%	9%	NA	NA	NA	NA	NA	The median survival is based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm.	2.
	Placebo+BSC	170	6%								
HRQoL Main analysis	Trifluridine/ tipiracil	337	2.6 months (2.3.3.3)	NA	NA	NA	HR:1.27	0.85-1.87	NA	Median time to deterioration by ≥ 5 points. QLQ-C30 GHS score. For the median time to deterioration in QoL, 95% confidence intervals (CI) were calculated; hazard ratios (HR) were calculated for between-group differences. Time to first deterioration in QoL was evaluated for each arm using Kaplan–Meier estimates and compared using the log-rank test. The main analysis of time to deterioration in QoL was defined as time to first deterioration by 5 points or more from baseline. Patients with no confirmed deterioration from baseline were censored at the time of their last observation. For this analysis, a Cox's proportional hazard model was used to adjust for baseline EORTC QLQ-C30 and LQSTO22scores, country and primary tumor type.	7, 8
	Placebo+BSC	170	2.3 months (1,4-not estimable)								

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Table A3a Results of study TAGS											
HRQoL Sensitivity analysis incl. death	Trifluridine/ tipiracil	337	3.19 months (2.80.3.82)	NA	NA	NA	HR:0.92	0.74-1.16	NA	Risk of deterioration by ≥ 10 points. (See page 11 for further information).	7.
	Placebo+BSC	170	2.27 months (2.07-3.36)								
HRQoL Sensitivity analysis incl. death or PD	Trifluridine/ tipiracil	337	NA	NA	NA	NA	NA	NA	NA	Risk of deterioration by ≥ 10 points. **QLQ-C30 and QLQ-STO22 scores. (See page 13 for further information).**	7.
	Placebo+BSC	170	NA								
Table A3a Results of study TAGS											
HRQoL Sensitivity analysis incl. death or PD	Trifluridine/ tipiracil	337	2.11 moths (2.07-2.27)	NA	NA	NA	NA	NA	NA	Risk of deterioration by ≥ 10 points. **QLQ-C30 GHS. (See page 13 for further information).**	7.
	Placebo+BSC	170	1.88 moths (1.84-1.94)								
Time to deterioration of ECOG PS≥2	Trifluridine/ tipiracil	337	4.3 months (3.7-4.7)	2.0	NA	NA	HR:0.69	0.562,0.854	0.0005	Pre-specified analysis of time to worsening ECOG performance status	2.
	Placebo+BSC	170	2.3 months (2.0-2.8)								

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NOT APPLICABLE: Not requested by Danish Medicine Council

Table A3b Results of study <y>	
Trial name:	*Insert trial name*
NCT number:	*Insert NCT number*

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Example: median overall survival	XXX	247	22.3 (20.3–24.3) months	4.9	1.79–8.01	0.002	HR: 0.70	0.55–0.90	0.005	*The median survival is based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm.*	
	ZZZ	248	17.4 (15.0–19.8) months								
Example: 1-year survival	XXX	247	74.5% (68.9–80.2)	10.7	2.39–19.01	0.01	HR: 0.70	0.55–0.90	0.005	*The survival rates are based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm.*	
	ZZZ	248	63.8% (57.6–70.0)								
	XXX	211	–1.5 (0.1–3.1)	4.5		0.05	NA	NA	NA		

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Table A3b Results of study <y>							
Example: HRQoL	ZZZ	209	−6.0 (−1.8 to −10.2)	−8.97 to −0.03		*The absolute difference in effect is estimated using a two-sided t-test.*	
Insert outcome 4	Intervention Comparator						
Insert outcome 5	Intervention Comparator						

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7.4 Results per PICO (clinical question)

Table A4 Results referring to <clinical question x>								
Results per outcome:	*Attach forest plots and statistical results as a separate file.* *Results from the comparative analysis should be given in the table below, if possible.*							
		Absolute difference in effect			**Relative difference in effect**			**Methods used for quantitative synthesis**
	Studies included in the analysis	**Difference**	**CI**	***P* value**	**Difference**	**CI**	***P* value**	

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Table A4 Results referring to <clinical question x>					

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Technical Report of Economic Models: Lonsurf® for the Treatment of Metastatic Gastric Adenocarcinoma in Patients Who Have Received At Least Two Prior Therapies, 98800.

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Abbreviations

Abbreviation	Definition
AE	Adverse event
BSA	Body surface area
BSC	Best supportive care
CSR	Clinical study report
CT	Computed tomography
DP	Disease progression
DSU	Decision Support Unit
GC	Gastric cancer
GEJ	Gastro-oesophageal junction
GP	General practitioner
HCP	Healthcare professional
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
KM	Kaplan–Meier
mGC	Metastatic gastric cancer
OS	Overall survival
OWSA	One-way sensitivity analysis
PD	Progressed disease
PFS	Progression-free survival
PLD	Patient-level data
PSM	Parametric survival model
ROW	Rest of the world
SD	Standard deviation
SmPC	Summary of product characteristics
TA	Technology appraisal
ToT	Time on treatment
TRTEDT	Treatment end date
TRTSDT	Treatment start date
TSD	Technical Support Document

The economic evaluation of treating mGC patients with Lonsurf *versus* best supportive care is based on the cost-effectiveness model developed by BresMed[1]. The model and technical report are provided as separate files along to the DMC. The original model has been adapted to the Danish setting by using Danish unit costs, only focusing on the cost part of the model and disregarding the effectiveness aspect of the model to be aligned with the pre-2021 guidelines from the Danish Medicines Council (DMC).The original model did not include a budget impact module, which has been added as part of adapting the model to the Danish setting. All the cost inputs and outputs are in DKK.

The guiding principle has been to use the Danish DRG takster 2021 and the publication Værdisætning af enhedsomkostninger-vers. 1.2 published by Medicinrådet January 31, 2020.

1. Patient population

For treatment of third line mGC and GEJ cancer (that is to say two prior lines of treatment) there is an unmet need, with a lack of evidence-based treatment options demonstrating benefit beyond BSC. The ESMO guidelines state treatment options may be used sequentially in second-line and third-line settings, but evidence is lacking for a survival benefit of chemotherapy beyond second-line treatment.[2]

After failure of second-line therapies, treatment options are scarce. The latest updated version of ESMO guidelines state that third-line chemotherapy with trifluridine/tipiracil is recommended for patients who are of Performance Score 0–1 [I, A].[4] For patients with 3L+ mGC in Europe, there is a lack of evidence from a European population for the effectiveness of currently used cytotoxic treatments and there is an absence of treatment options which offer a survival advantage and/or improved QoL. [2,3]

Furthermore, progress in therapy has been minimal in recent years and multiple phase III trials in mGC have not met their primary endpoints.[5] Immuno-oncology therapies that have demonstrated OS benefits in many other tumour types have failed to demonstrate significant OS improvements in mGC, due to the aggressive and rapidly progressing nature of the disease.

Danish clinical practice: In Denmark there is currently no recommended third-line palliative chemotherapy for metastatic gastro-oesophageal cancer.[6] If approved, trifluridine/tipiracil would provide a treatment option for adult patients with mGC or GEJ adenocarcinoma previously treated with at least two prior lines of chemotherapy.

Clinical documentation submitted (in relation to clinical practice): The patient population in the cost-effectiveness analysis considers the patient population of adult patients with metastatic gastric adenocarcinoma, including GEJ adenocarcinoma, who have received at least two prior therapies for metastatic disease. This is in line with the patient population included in the TAS-102-302 TAGS study.

Table 1 - Subgroups considered in the model

Subgroup label	N	Study population
ITT (base case)	507	Intention-to-treat population, from TAS-102-302 TAGS trial
ITT, no prior ramucirumab	338	Intention-to-treat population who did receive a prior ramucirumab treatment, from TAS-102-302 TAGS trial
ROW, no prior ramucirumab	322	Rest of world population who did not receive a prior ramucirumab treatment, from TAS-102-302 TAGS trial
Key: ITT, intention-to-treat; N, number; ROW, rest of world		

Model submitted (according to clinical documentation and clinical practice):
The cost-effectiveness model for Lonsurf® (T/T, trifluridine/tipiracil or trifluridine/tipiracil hydrochloride) in the treatment of adult patients with metastatic gastric adenocarcinoma, including gastroesophageal junction adenocarcinoma, who have received at least two prior therapies for metastatic disease. The cost-effectiveness model is a partitioned survival model comparing the costs and health outcomes associated with Lonsurf® treatment to the costs and health outcomes associated with best supportive care. Efficacy inputs are based on analyses of the Phase III TAS-102-302 TAGS trial[7], providing evidence for the efficacy of Lonsurf® compared with best supportive care as a third-line and beyond treatment in metastatic gastric cancer.

2. Description of the intervention

Lonsurf® (trifluridine/tipiracil), L01BC59, is indicated as monotherapy for the treatment of adult patients with metastatic gastric cancer including adenocarcinoma of the gastroesophageal junction, who have been previously treated with at least two prior systemic treatment regimens for advanced disease[8].

Intervention:

Lonsurf (trifluridine / tipiracil): 35 mg / m^2 / dose administered orally twice daily on days 1 to 5 and day 8 to 12 of each 28-day cycle, as long as therapeutic benefits are observed or until unacceptable toxicity occurs (SmPC). The study drug tablet calculation is presented in Table 2, which shows the number of tablets that are needed per calculated body surface area (BSA). Treatment with Lonsurf may be continued until progression, toxicity, patient refusal, physician's decision, or pregnancy. In case of toxicity, patients are permitted dose reduction(s) to a minimum dose of 20mg/m^2 in 5mg/m^2 decrements. Following a reduction, the dose of Lonsurf cannot be increased again. If the dose reduction to 20mg/m^2 fails to achieve the minimal criteria to resume treatment or if toxicities recur after the dose reductions, treatment is discontinued.

Table 2 - Dose banding scheme from Lonsurf SmPC[8]

BSA	Dose per administration (mg) (twice daily)	Tablets per administration		Dose per treatment cycle
		15mg	20mg	
<1.07	35	1	1	700
1.07–1.22	40	0	2	800
1.23–1.37	45	3	0	900
1.38–1.52	50	2	1	1000
1.53–1.68	55	1	2	1100
1.69–1.83	60	0	3	1200
1.84–1.98	65	3	1	1300
1.99–2.14	70	2	2	1400
2.15–2.29	75	1	3	1500
≥2.30	80	0	4	1600
Key: BSA, body surface area; SmPC, summary of product characteristics.				

In the TAGS clinical trial, the distribution of patients by dose administrated, by cycle of treatment was as follows (Table 3):

Table 3 - Distribution of patients by actual dose taken, by cycle, in trifluridine/tipiracil arm

Cycle	N	Trifluridine/tipiracil (N=335), n (%)			
		35 mg/m²	30 mg/m²	25 mg/m²	20 mg/m²
1	334	334 (100.00)			
2	279	255 (91.40)	24 (8.60)		
3	144	127 (88.19)	17 (11.81)		
4	115	99 (86.09)	13 (11.30)	3 (2.61)	
5	65	47 (72.31)	15 (23.08)	3 (4.62)	
6	53	38 (71.70)	11 (20.75)	3 (5.66)	1 (1.89)
7	30	19 (63.33)	8 (26.67)	1 (3.33)	2 (6.67)
8	27	17 (62.96)	6 (22.22)	2 (7.41)	2 (7.41)
9	21	13 (61.90)	6 (28.57)	1 (4.76)	1 (4.76)
10	16	9 (56.25)	6 (37.50)		1 (6.25)
11	10	5 (50.00)	4 (40.00)		1 (10.00)
12	5	2 (40.00)	3 (60.00)		
13	2	1 (50.00)	1 (50.00)		
14	1		1 (100)		

In a different analysis it is also possible to ascertain the distribution of patients by dose intensity (Table 4).

Table 4 - Distribution of patients by fraction of the target dose, by treatment arms.

Cycle	Fraction of the target dose	N (T/T)	Trifluridine/tipiracil (N=335)
1	<80%	334	26 (7.8)
	≥80%		308 (92.2)
	≥90%		304 (91.0)
	>100%-120%		1 (0.3)
2	<80%	279	18 (6.5)
	≥80%		261 (93.5)
	≥90%		257 (92.1)
3	<80%	144	8 (5.6)
	≥80%		136 (94.4)
	≥90%		135 (93.8)
4	<80%	115	2 (1.7)
	≥80%		113 (98.3)
	≥90%		112 (97.4)
5	<80%	65	4 (6.2)
	≥80%		61 (93.8)
	≥90%		61 (93.8)
6	<80%	53	2 (3.8)
	≥80%		51 (96.2)
	≥90%		50 (94.3)
7	<80%	30	0
	≥80%		30 (100)
	≥90%		30 (100)
8	<80%	27	0
	≥80%		27 (100)
	≥90%		27 (100)
9	<80%	21	1 (4.8)
	≥80%		20 (95.2)
	≥90%		20 (95.2)
10	<80%	16	0
	≥80%		16 (100)
	≥90%		16 (100)
11	<80%	10	2 (20.0)
	≥80%		8 (80.0)
	≥90%		8 (80.0)
12	<80%	5	0
	≥80%		5 (100)
	≥90%		5 (100)

Cycle	Fraction of the target dose	N (T/T)	Trifluridine/tipiracil (N=335)
13	<80%	2	0
	≥80%		2 (100)
	≥90%		1 (50.0)
14	<80%	1	0
	≥80%		1 (100)
	≥90%		1 (100)
15	<80%	0	0
	≥80%		0
	≥90%		0
16	<80%	0	0
	≥80%		0
	≥90%		0

Drug acquisition costs per year for trifluridine/tipiracil and alternative treatments are calculated by the model based on the drug acquisition costs per month and the mean months on treatment. Mean on months on treatment for trifluridine/tipiracil is set at three months, which is derived from the TAS-102-302 TAGS trial.

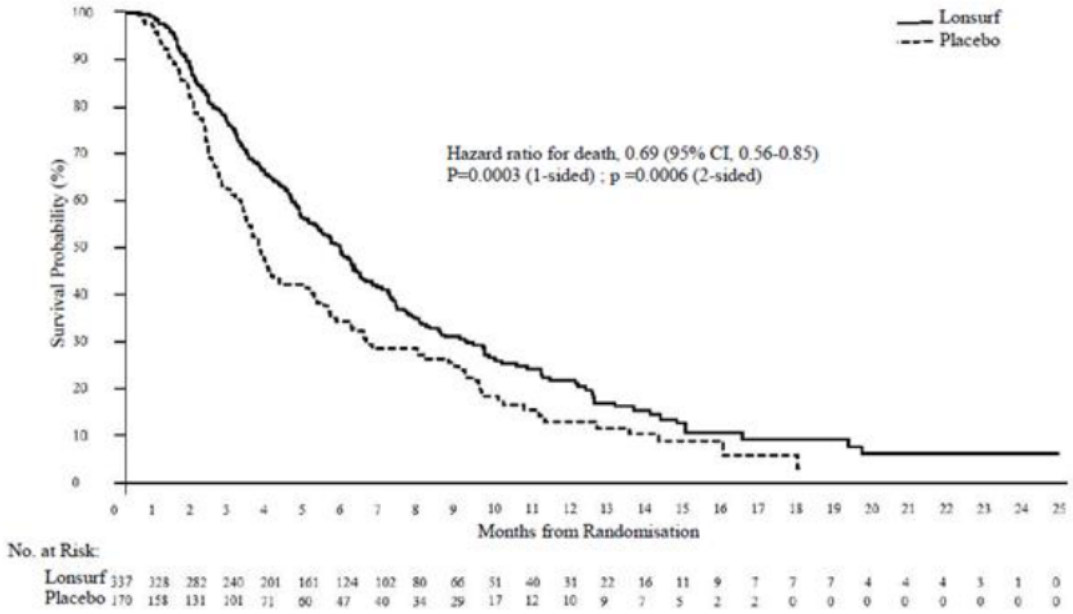
2.1 Overall survival results[7]

In the TAGS trial, the primary endpoint of OS was met, with the risk of death statistically significantly lower by 31% in the FTP/TPI group compared to the placebo group (HR: 0.69; 95% CI: 0.56–0.85, one-sided p=0.0003, two-sided p=0.0006). The data demonstrates that 47% of all patients in the trifluridine/tipiracil group were alive at 6 months (versus 33% in the placebo group) and 21% alive at one year (versus 13% in the placebo group).

For OS, results obtained for all stratification factors and most subgroups were consistent with those obtained for the ITT population. The Hazard ratios (HR) consistently favor the trifluridine/tipiracil group with only 2 exceptions noted of the 49 subgroups examined (patients who did not receive taxane; patients with well-differentiated tumors). Both subgroups comprised a small number of patients (48 and 46, respectively), each accounting for less than 10% of the population. In both cases, corresponding PFS results clearly favored the trifluridine/tipiracil group. Multivariate analysis did not identify prior taxane use as a prognostic or predictive factor; while histology subtype showed some prognostic value, it did not demonstrate any predictive effect.

The corresponding Kaplan-Meier curves overlapped for the 2 groups and crossed at times, making the HR estimate unreliable. A supportive multivariate analysis was performed for prior treatment with taxane and irinotecan (yes or no), which did not identify prior taxane or irinotecan use as a prognostic or a predictive factor.

Figure 1 - Kaplan-Meier curves of overall survival in TAGS[7]



New exploratory subgroup analysis of the TAGS study[9]

Additionally, a new exploratory subgroup analysis has been conducted on the TAGS study, confirming the previous results and the therapeutic value of Lonsurf (Tabernero et al. 2021). The aim of the analysis was to separately assess the efficacy, safety and quality of life of trifluridine/tipiracil (FTD/TPI) when given in the third-line setting (3L) or fourth/later-line setting (4L+) versus placebo.

In this analysis, the median overall survival (mOS) was significantly longer in patients treated with FTD/TPI than with placebo in both the 3L group and the 4L+ group. When considering the overall population of the TAGS study the difference in OS was 2.1 months in favour of patients receiving FTD/TPI compared to those receiving BSC/placebo. With the updated analysis presented at ASCO GI 2021 the difference in the subgroup of patients treated with FTD/TPI compared to BSC/placebo in the 3rd line setting is even greater with 3.6 months. The results are presented in Table 5.

Table 5 - Results of the exploratory subgroup analysis of TAGS study

3L patients					
	FTD/TPI	**BSC/Placebo**	**HR**	**CI 95%**	**P-value**
OS	6.8	3.2	0.67	0.47–0.97	0.0318
PFS	3.1	1.9	0.54	0.38–0.77	0.0004
4L+ patients					
OS	5.2	3.7	0.72	0.55–0.95	0.0192

PFS	1.9	1.8	0.57	0.44–0.74	< 0.0001
Overall population					
OS	5.7	3.6	0.69	0.56–0.85	0.0006
PFS	2.0	1.8	0.57	0.47–0.70	< 0.0001

Source: (Tabernero et al. 2021)

Key: FTD/TPI, trifluridine/tipiracil, HR, Hazard ratio, CI, Confidence interval, OS, Overall survival, PFS, Progression-free survival, 3L, third-line setting, 4L+, fourth/later-line setting.

Specific adverse events occurred at similar rates in the two groups. Although there was a slightly higher incidence of adverse events related to immunosuppression in the 3L group than the 4L+ group, this was not considered inconsistent with the overall study population. There were no clinically significant deteriorations by ≥5 points in the mean QLQ-C30 total score or any subscale scores in either arm of the 3L group or the 4L+ group.

This subgroup analysis confirms the previously reported results and strengthens the scientific evidence of Lonsurf in the treatment of mGC, with a larger survival benefit in 3L. Results of quality of life in both 3L and 4L+ were consistent with previously published subgroup analyses and with the overall TAGS study population.

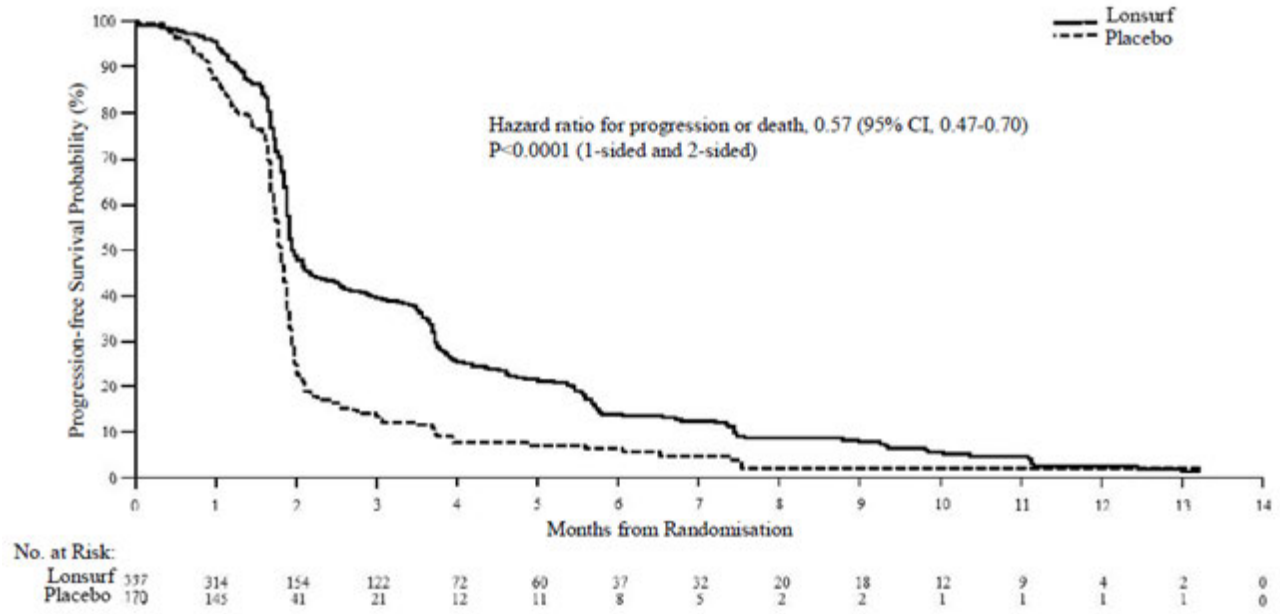
2.2 Progression free survival results[7]

The addition of trifluridine/tipiracil to BSC resulted in a statistically significant improvement in PFS compared to placebo plus BSC, with an HR of 0.57 (95% CI: 0.467, 0.701), corresponding to a 43% reduction in risk of disease progression. The median PFS was 2.0 months for the trifluridine/tipiracil group versus 1.8 months for the placebo group (1-sided and 2-sided $p < 0.0001$; stratified log-rank test).

Although the difference in median PFS was small, the percentage of patient's progression free was consistently higher for the trifluridine/tipiracil group than for the placebo group, starting at the time of the initial post baseline tumor assessment at 2 months (FTP/TPI: 49.7%; placebo: 25.3%). The percentage of patient's progression free at 4 and 6 months, respectively was 27% and 15% for the trifluridine/tipiracil group and 8% and 6% for the placebo group.

As shown in Figure 2 , the separation of the PFS curves for trifluridine/tipiracil and placebo was maintained starting from the time of the initial tumor assessment.

Figure 2 - Kaplan-Meier curves of progression free survival in TAGS[7]



3. Comparator(s)

Pharmaceutical form: Placebo + Best Supportive care.[7]

4. Perspective and visibility of consequences for different actors

The economic analysis is based on a societal perspective. The model includes costs of caregiver's time off work and patients' transport costs. Costs of caregiver's time off work consider the costs of caregivers looking after patients. The costs are based on the assumptions made for the proportion of working caregivers, average hourly wage, average working hours per week, the proportion of patients who require a carer and the average days of care required for a patient. A working week is assumed to be 37 hours at a DKK 179 hourly wage. The base case assumption of 50% of caregivers working and an average of 2.4 working days per week is based on UK cancer caregiver survey: Macmillan Cancer Support. The Rich Picture on carers of people with cancer. 2016. Available at: https://www.macmillan.org.uk/_images/carers-of-people-with-cancer_tcm9-282780.pdf. Accessed: June 1, 2021. Patients' production loss is not included because it is very unlikely that mGC patients in their third or later line of treatment still work.

Transportation costs are added for patients who travel for treatment by their own car. The frequency of travel is based on the frequency of outpatient visits. The original model had 2 components, km and price per km. In the Danish model the input is 10 km at DKK 10.00 which come to the amount of DKK 100 according with the Danish costing instructions

5. Time horizon

In the base case, the time horizon is set at 10 years, which is the traditional life-time horizon used in health economic evaluation in cancer. The time horizon in the model is user definable. The impact of shorter time horizons (2, 3, 4 and 5 years) is tested in scenario analyses.

Cycle length

The model uses a weekly cycle length. This cycle length is not user definable.

Discounting

Discounting was according to "Metodemetodevejledning for omkostningsanalyser af nye lægemidler og indikationer i hospitalssektoren" set to 3.5%, which is the current recommendation by the Danish Ministry of Finance. The discount rate of LYs is set at 0%.

6. Model inputs

6.1 Patient characteristics

Patient characteristics that are used as model inputs are presented in Table 6.

Table 6 - Patient characteristics used in the model

	ITT N = 507		**ROW N = 434**		**ITT, no prior ramucirumab N = 338**		**ROW, no prior ramucirumab N = 322**	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age	62.51	10.52	61.84	10.77	61.83	11.10	61.52	11.14
BSA	1.75	0.21	1.77	0.21	1.77	0.20	1.78	0.20
Percentage of patients male	0.73	0.01	0.72	0.01	0.72	0.01	0.73	0.01
Key: BSA, body surface area; ITT, intention-to-treat; N, number; ROW, rest of world; SD, standard deviation								

Patient characteristics in Table 6 of the Lonsurf and BSC treatment arms, corresponding to each subgroup available in the model. As the base case model uses the 'ROW, no prior ramucirumab' subgroup, the base case model uses the patient characteristics of this subgroup.

6.2 Efficacy

Efficacy inputs for the model include data on the survival outcomes OS, PFS and time on treatment (ToT), as well as data on adverse events (AEs). All efficacy inputs for Lonsurf and BSC are derived from the TAS-102-302 TAGS trial.

6.2.1.1 Approach to survival extrapolation

To extrapolate each survival outcome, 'standard' parametric survival models (PSMs), as described in NICE TSD DSU 14[10] (referred to hereafter as TSD 14), are fitted to the following endpoints for both Lonsurf and BSC:

- OS
- PFS
- ToT

The following six parametric curves were fitted:

- Exponential
- Weibull
- Gompertz
- Log-logistic
- Log-normal
- Generalised gamma

All parametric models are fit using the 'flexsurv' package in R using the flexsurvreg function[11,12]. For all options in which PSMs are fitted to the Kaplan–Meier (KM) data, both stratified and unstratified parametric curves are fitted to the data and are included as options in the Excel model. An unstratified PSM jointly estimates the survival for Lonsurf and BSC within one model, taking treatment effect into account. In contrast, a stratified PSM means that separate models are fitted to each treatment separately. However, as patient-level data (PLD) are available for the TAS-102-302 TAGS trial, stratified models may be preferred, as per guidance given in TSD 14: 'Generally, when PLD are available, it is unnecessary to rely upon the proportional hazards (PHs) assumption and apply a PHs modelling approach'. For this reason, only stratified models are further considered in this technical report.

The following methods were used to assess the model fit/plausibility to aid selection of survival curves to be used as the base case in the economic model:

- Visual inspection
  - The fitted survival curves were overlaid on KM data to assess how closely the curves match the observed data. This is an important consideration as although visual inspection is subjective, it allows for judgement on curves that fit the most important parts of the survival curves – i.e. those with most data
- Goodness of fit measures: Akaike information criteria (AIC) and Bayesian information criterion (BIC)

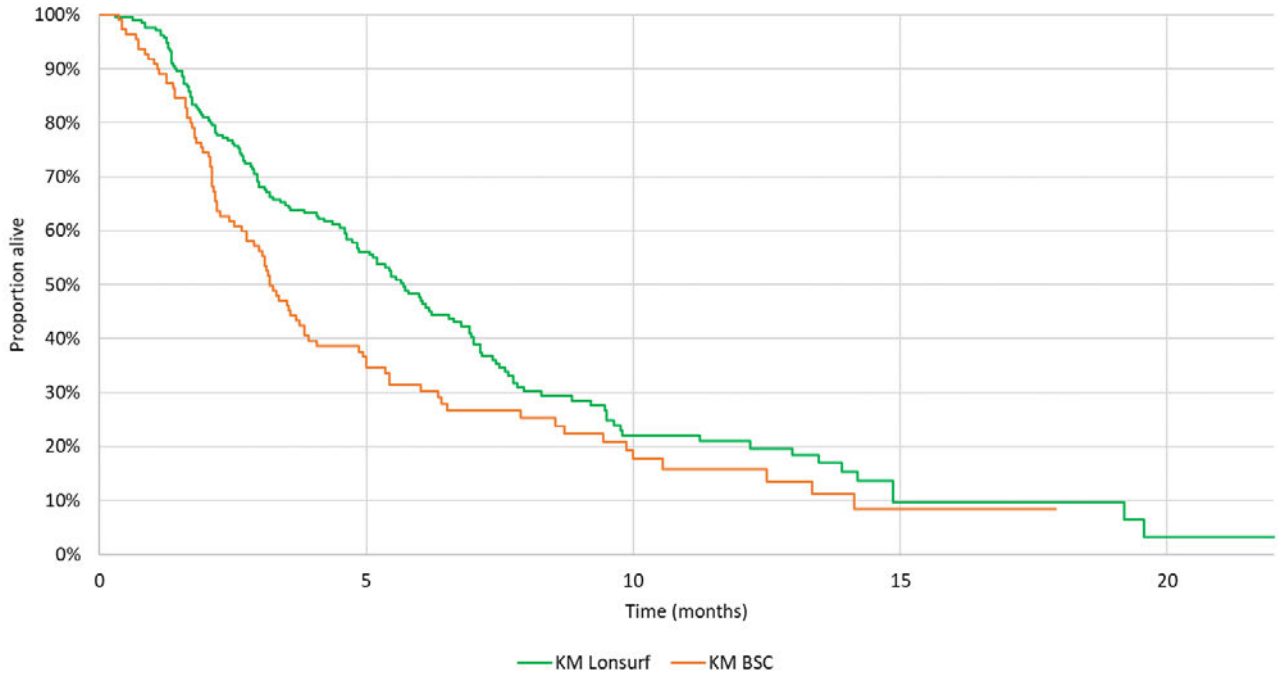
– The lower the AIC or BIC, the better the model fit to the observed data. A nominal difference of approximately at least five in AIC and/or BIC is considered to imply a meaningful difference in the fit of the PSMs to the observed data

In cases where the 'standard' parametric methodology presented above did not provide a good fit the KM estimates, alternative methods were considered. These are described in detail in the following sections.

6.2.1.2 Overall survival

OS was the primary endpoint of this study and was defined as the time from the date of randomisation to the date of death. If death was not observed during the study, the time was censored at either the last date the patient was known to be alive or the cut-off date, whichever occurred earlier. The cut-off date for OS was defined by the date of the 384th death (27 March 2018). Patients having a documented survival status (alive or dead) after this date were censored at the cut-off. With the OS cut-off date being event driven, for operational efficiency, the cut-off date for all other study endpoints was fixed at a similar date to the OS cut-off date, when the milestone neared completion. The clinical cut-off date for all endpoints other than OS was fixed as of 31 March 2018.[7] Figure 3 presents the overall survival KM of the 'ROW, no prior ramucirumab' population for Lonsurf and BSC, as observed in the TAS-102-302 TAGS trial.

Figure 3 - Lonsurf and BSC KM – OS



Time (months)	0	5	10	15	20
N at risk: Lonsurf	211	98	24	5	1
N at risk: Placebo	111	34	11	2	0

Key: BSC, best supportive care; KM; Kaplan–Meier; N, number; OS, overall survival

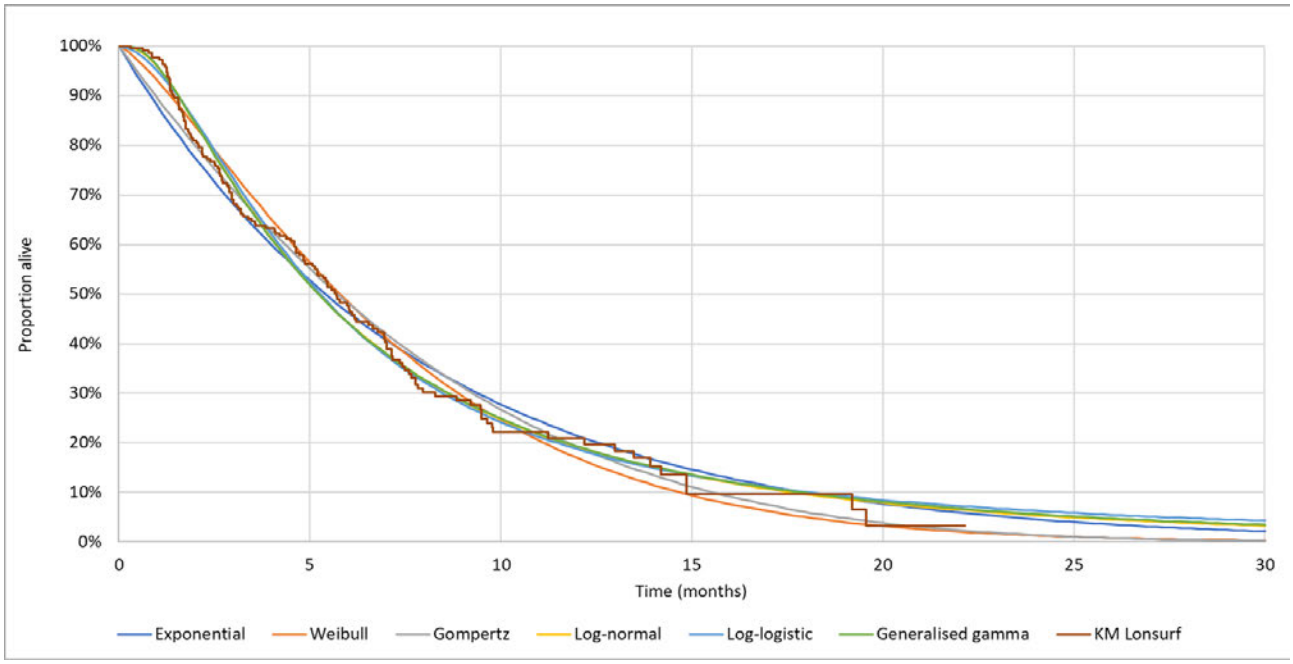
The six stratified parametric curve fits to the OS KM data and are presented in Figure 4 and Figure 5. The PSMs' AIC and BIC statistical fit parameters are presented in Table 7, where a lower number means a better fitting model. The mean and median OS estimates associated with each PSM are presented in Table 8. The log-normal was considered to have the best statistical fit. As it also had a good visual fit, the log-normal curve was used in the base case analysis (Figure 4 and Figure 5). The plausibility of the estimated OS curves is supported by the maturity of the data, the overlap between the estimated curves and the observed OS as well as the estimated OS curves are consistent with the natural history of late stage mGC.

As the OS in these data is mature, another approach is included as an option in the Excel model: the use of KM data until a user-amendable cut-off point and the use of PSM for the rest of the data. The model uses 20% of patients still alive as the cut-off point. This option uses the same PSMs as presented in Figure 2 and Figure 3, with the same associated AIC and BIC statistical fit parameters as presented in Table 7. Whenever the KM data are used directly in the model, the uncertainty around the KM is captured within sensitivity analyses by a pragmatic solution referred to as the 'Greenwood method'. Here, Greenwood's[14] 95% confidence intervals of the OS KM are used to calibrate a normally distributed HR which can be applied to the KM curve. Calibration of the HR is done by increasing or decreasing the standard deviation (SD). For deterministic scenario analysis, the model sets the HR to its lower and upper bound to evaluate extreme, yet plausible survival estimates and to measure the impact on the ICER.

Given the data are mature and the standard curves fit the KM data well, no further models were considered for OS.

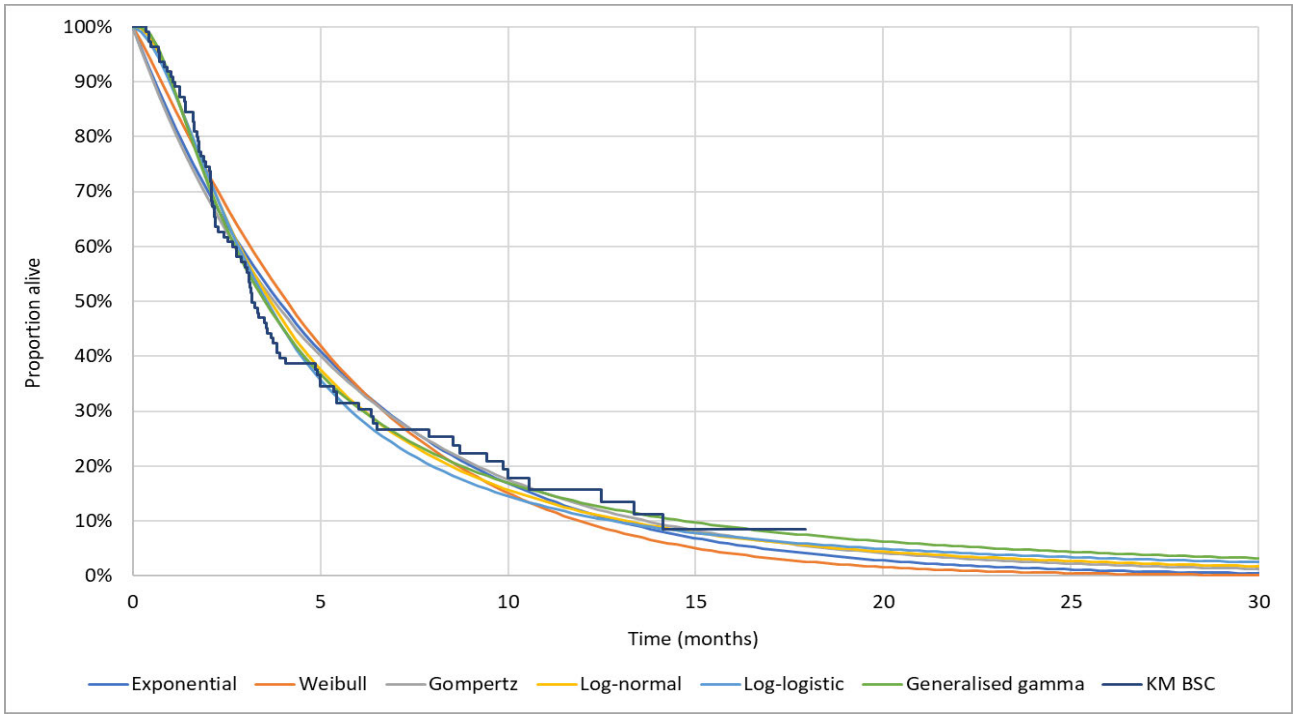
Whenever mortality rates from the TAS-102-302 TAGS trial are exceeded by age-specific mortality rates observed in the general population, the model uses general population mortality rates. In the base case model, this functionality is not in use, because the TAS-102-302 TAGS trial mortality rates are never exceeded by the general population mortality rates.

Figure 4 - Lonsurf PSM / curve fits and KM – OS



Key: KM, Kaplan–Meier; OS, overall survival; PSM, parametric survival model

Figure 5 - BSC PSM / curve fits and KM – OS



Key: BSC, best supportive care; KM, Kaplan–Meier; OS, overall survival; PSM, parametric survival model

Table 7 - Lonsurf and BSC PSM statistical fit parameters – OS

	Lonsurf		BSC	
Model	**AIC**	**BIC**	**AIC**	**BIC**
PSM				

Exponential	906.2060	909.5579	481.5783	484.2879
Weibull	894.6547	901.3584	481.7283	487.1474
Gompertz	904.7563	911.4600	483.2202	488.6392
Log-normal	**881.5111**	**888.2148**	**466.6428**	**472.0618**
Log-logistic	887.1870	893.8907	468.0245	473.4435
Generalised gamma	883.4950	893.5505	467.4145	475.5431
Key: AIC, Akaike information criteria; BIC, Bayesian information criterion; BSC, best supportive care; OS, overall survival; PSM, parametric survival model.				

Figure 6 – Lonsurf modelled versus observed OS curves

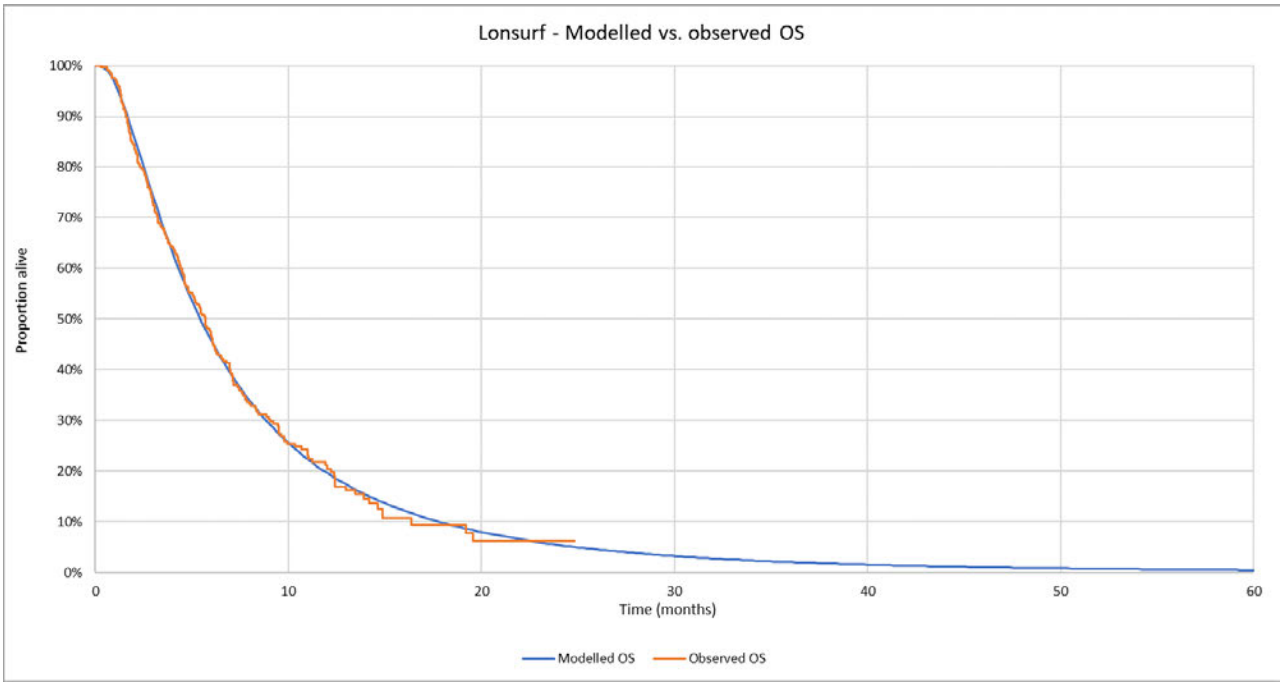


Figure 7 - BSC modelled versus observed OS curves

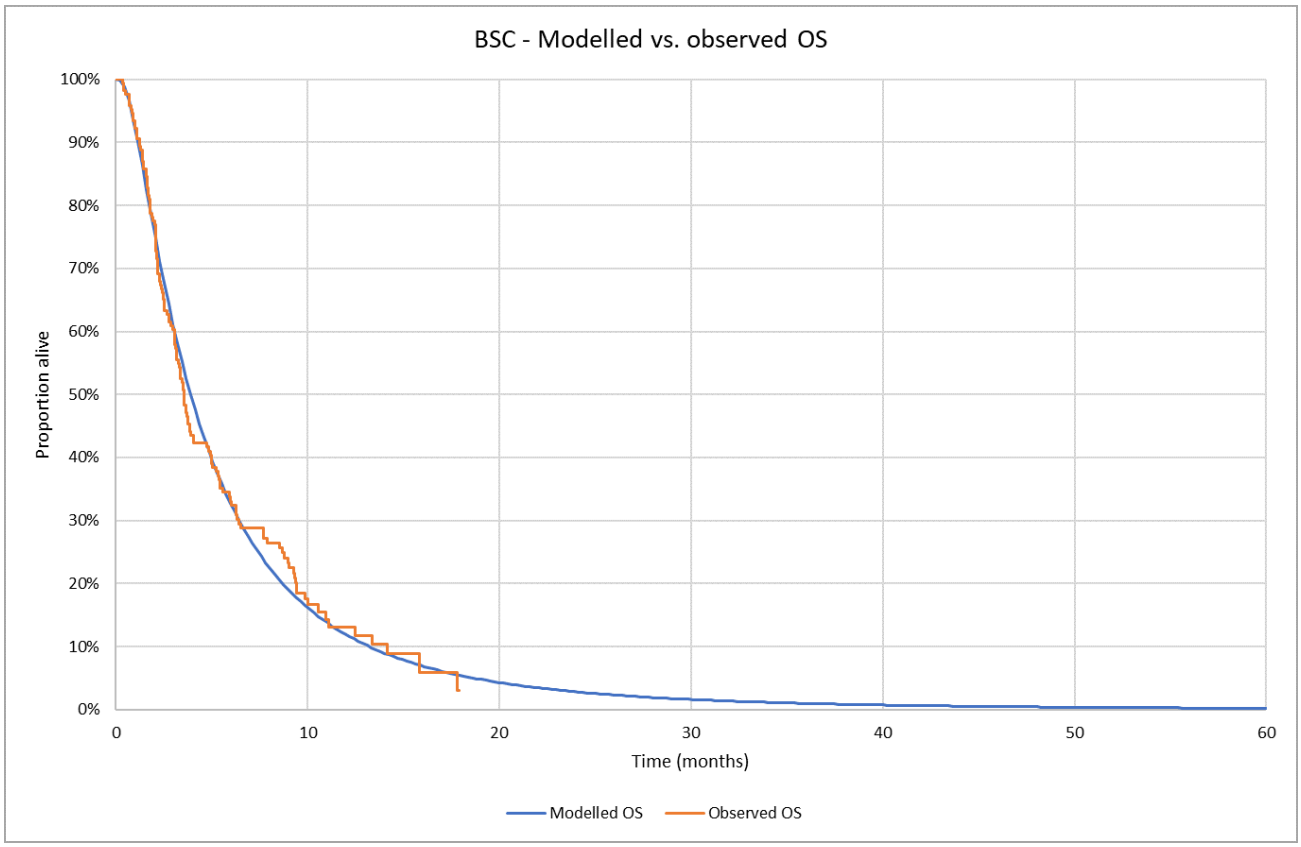


Table 8 - Lonsurf and BSC – median and mean OS

	Median OS (life years)		Mean OS (life years)	
Model	**Lonsurf**	**BSC**	**Lonsurf**	**BSC**
PSM				
Exponential	0.44	0.31	0.66	0.48
Weibull	0.48	0.33	0.60	0.46
Gompertz	0.46	0.31	0.61	0.50
Log-normal	0.42	0.29	0.69	0.51
Log-logistic	0.42	0.29	0.75	0.54
Generalised gamma	0.42	0.29	0.70	0.58
KM + PSM				
Exponential	0.46	0.25	0.67	0.49
Weibull	0.46	0.25	0.61	0.47
Gompertz	0.46	0.25	0.61	0.52
Log-normal	0.46	0.25	0.72	0.54
Log-logistic	0.46	0.25	0.79	0.61
Generalised gamma	0.46	0.25	0.72	0.62
Key: BSC, best supportive care; OS, overall survival; PSM, parametric survival model				

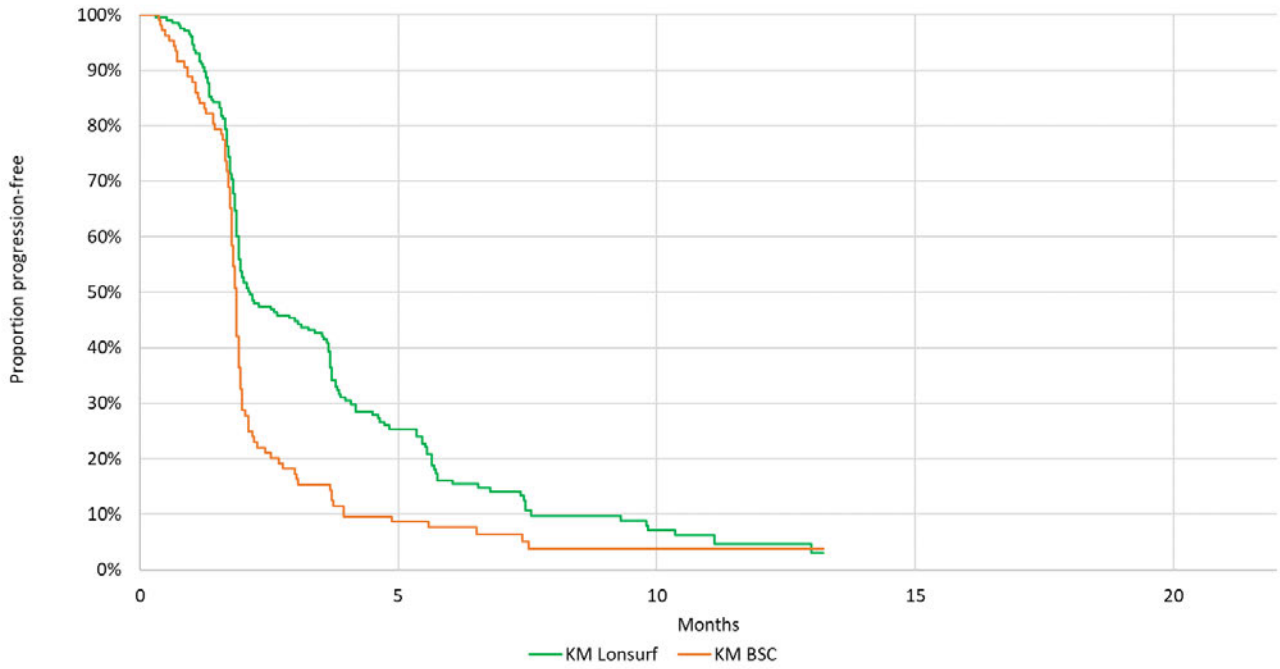
Treatment effect duration

In the model, the user can cap the OS treatment effect duration of Lonsurf versus BSC by choosing a shorter time horizon for the analysis.

6.2.1.3 Progression-free survival

PFS was a key secondary endpoint of this study and was defined as the time from the date of randomisation to the first occurrence of radiological progression or death. PFS was based on investigator assessment of radiological images, performed at baseline and every 8 weeks[13]. Figure 8 presents the PFS KM of the 'ROW, no prior ramucirumab' population for Lonsurf and BSC, as observed in the TAS-102-302 TAGS trial.

Figure 8 - Lonsurf and BSC KM – PFS



Time (months)	0	5	10
N at risk: Lonsurf	211	40	8
N at risk: Placebo	111	9	1

Key: BSC, best supportive care; KM; Kaplan–Meier; N, number; PFS, progression-free survival

The six stratified parametric curve fits to the PFS KM data are presented in Appendix 1: Progression-free survival model methods. These curves do not fit well to the KM, especially in the first 8 weeks of the data. This is largely due to the steep drop at the time of the first progression assessment. These steep drops are more evident in the KM curve for the BSC treatment arm.

To address the large drop at the first assessment (8 weeks), piecewise modelling was explored as another option by using the KM until 8 weeks and then PSM curves fitted to the rest of the data (i.e. re-based PSM curves), presented in Appendix 2: KM + re-based PSM / curve fits. The figures show that this approach provides a much better fit to the KM than standard PSM curves, especially for the BSC arm. In the Lonsurf arm the large drops in the KM continue at further time points that correspond to the next progression assessments but to a lesser extent than the first assessment, as there are fewer patients at risk in later assessments. The re-based fits do not model these smaller drops particularly well, but the overall visual fit is still reasonable using this re-based method. Table 9 provides an overview of the statistical fit parameters of the standard and re-based PSMs. The mean and median PFS estimates associated with each PSM are presented in Table 10.

As the PFS data are largely mature, a third option is included in the Excel model: using the KM data until a user-amendable cut-off point, and then using the PSM thereafter. The default cut-off point for this option is set to 20% of patients still not progressed.

The model also includes a fourth option, in which only KM data are used. As the PFS KM data are not fully mature, this method assumes that all patients progress or die after the last observed KM point, with no extrapolation.

The base case model uses the fifth option, which is called the interval censoring adjustment method. This method is described below.

Interval censoring adjustment method

Standard methods for time-to-event data analysis assume disease progression occurs at the time of the assessment visit. However, in real life, the exact point at which a patient experiences disease progression (DP) occurs sometime along the time interval, ranging from the previous assessment visit (where DP was not yet observed) and the subsequent assessment visit, where DP is observed/confirmed for the first time. Interval censoring is said to occur when the event of interest, T_i, for individual i does not happen at the exact time of the assessment visit but anytime during the interval between two visits, L_i and U_i. In this case, the only information available is that $L_i < T_i \leq U_i$.

Generally speaking, interval censoring is not a concern if the time interval between two succeeding assessment visits is short in relation to the event rate, e.g. DP. Interval censoring becomes a concern whenever a single time interval is accountable for a large proportion of DP events. This is the case of TAS-102-302 TAGS trial because time intervals are relatively long in comparison to the rate of DP. Hence, a large proportion of patients experience DP during the first-time interval. Since so many patients have their DP confirmed at the time of the very first assessment visit (8 weeks after randomization), the PFS KM curve shows a steep drop at 8 weeks. Moreover, the bias induced by interval censoring is also noticeable in successive assessment visits (e.g. at the time of the second assessment visit). NICE TSD 14[10] suggests that under these circumstances, statistical interval-

censored techniques should be considered to adjust for the bias induced by the overestimation of interval-censored PFS data.

Two variables from the response dataset were utilized to derive the interval-censored dataset: U_i and L_i. The first variable corresponds to the date when the patients' response was confirmed as DP: U_i (i.e. same as for standard approach). The second variable corresponds to the date of the previous response assessment visit, where the patients' response was still not DP: L_i. The time period between L_i and U_i is the interval when the event occurred for patient i. Data from the response dataset were formatted as follows:

- For patients who died without confirmed DP (uncensored data):
  - L_i = U_i = survival time
  - Event variable = 1
- For patients who have not progressed or died during the study (right-censored data):
  - L_i = time elapsed to last visit
  - U_i = infinite time
  - Event variable = 0
- For patients who have progressed (interval-censored data):
  - L_i = time elapsed to last visit showing no progression
  - U_i = time elapsed to first visit showing disease Progression
  - Event variable = 3

For the KM based estimations, the Non-Parametric Maximum Likelihood Estimator (NPMLE), often referred as the Turnbull's Estimator, was used to estimate the time-to-event distribution. The NPMLE can take the form of any proper survival function S that maximizes the likelihood function; and the likelihood is numerically maximized using the expectation-maximization algorithm. In R the survfit function is used to derive the KM estimate of the survival curve. The survival model is defined using the function Surv(time, time2, event, type="interval") where the survival events are assumed to have occurred between time and time2. The interval varies between individual and this information is used to estimate the KM curve.

For the parametric estimations, in order to extrapolate each PFS curve (while adjusting for the bias induced by interval censoring observed in TAS-102-302 TAGS trial), 'standard' parametric survival models were fitted using flexsurvreg function (available for the flexsurv R package)[15]. This approach is described by Collett (*2015*)[16] and involves maximizing a likelihood equation, where the event probability is modelled between $L_i \; and \; U_i$, rather than at a fixed time (as in the case of the standard approach). There are no further assumptions made by interval-censored adjustment methods beyond standard methods. The maximum likelihood estimator is solved after selecting a probability density function for the event of interest (i.e. exponential, Weibull, Gompertz, log-logistic, log-normal or generalised gamma). Following the fitting of the selected parametric survival model to the interval-censored data, the output of the likelihood function provides the corresponding parameter estimates

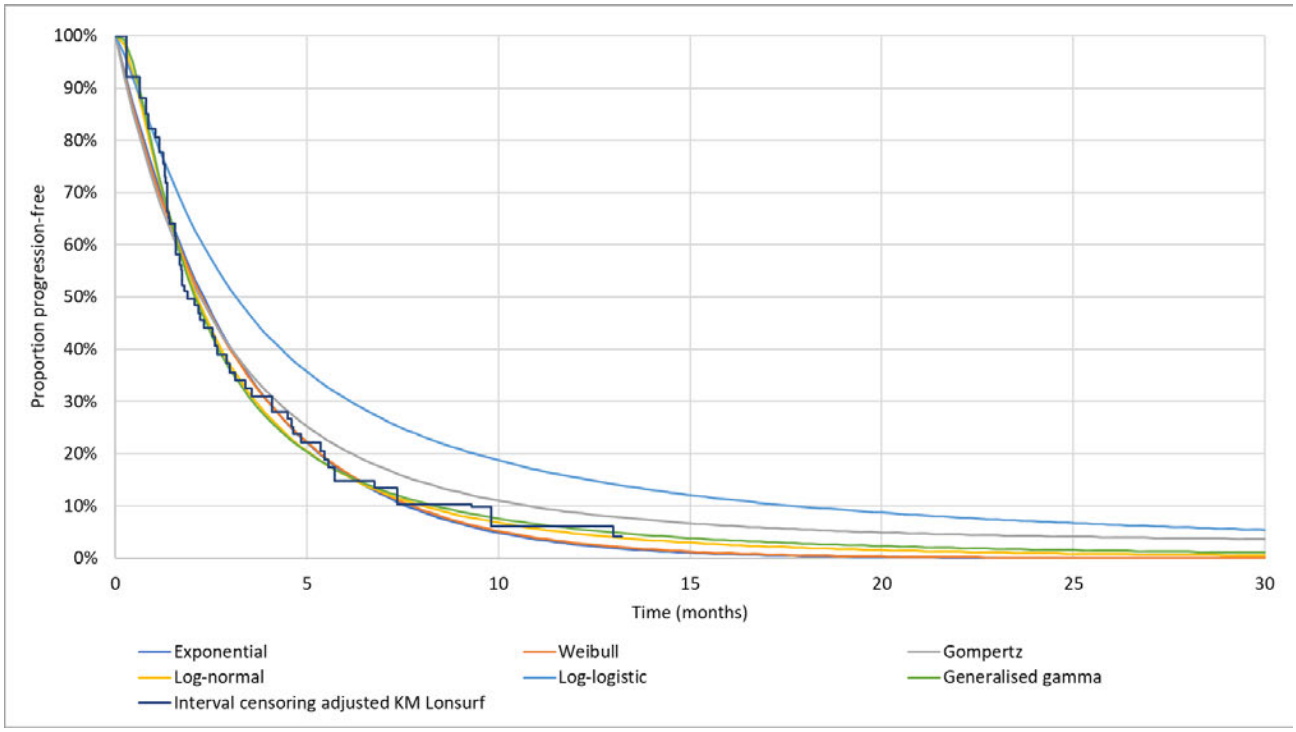
(for example, shape and scale for the Weibull distribution). Then, the adjusted interval-censored parametric curve is operationalized in the Excel model in the same way as other standard curves.

For PFS, the base case analysis applies this interval censoring adjustment method to limit the bias resulting from interval censoring. These fits are presented in Figure 9 and Figure 10. The AIC and BIC statistical fit parameters are presented in Table 9, where a lower number means a better fitting model. From the interval censoring-adjusted PSM, the log-normal has the best statistical fit so was used as the base case curve. The percentages of patients being progression free after 1–3 years with each interval censoring-adjusted PSM, and for each of the other PFS model options, are presented in Appendix 3: Lonsurf and BSC PSM / percentage of patients progression free at selected time horizons.

Figure 11 and Figure 12 present the best fitting re-based PSM curves and the interval censoring-adjusted curves. This graph shows how the interval censoring 'smooths' out the steps in the original KM and fits to the bottom-left corners of the original KM. The interval censoring adjustment method is likely to give a more realistic representation of PFS; however, it is not possible to test this assumption as it is unknown when exactly the patients progressed. Since the first step at 8 weeks is much larger in the BSC arm than in the Lonsurf arm (due to patients progressing quicker on BSC), the difference between the interval censoring-adjusted curve and the re-based PSM curve for BSC is larger for BSC than for Lonsurf. This could be viewed as a non-conservative approach, which should be acknowledged as a limitation of this method.

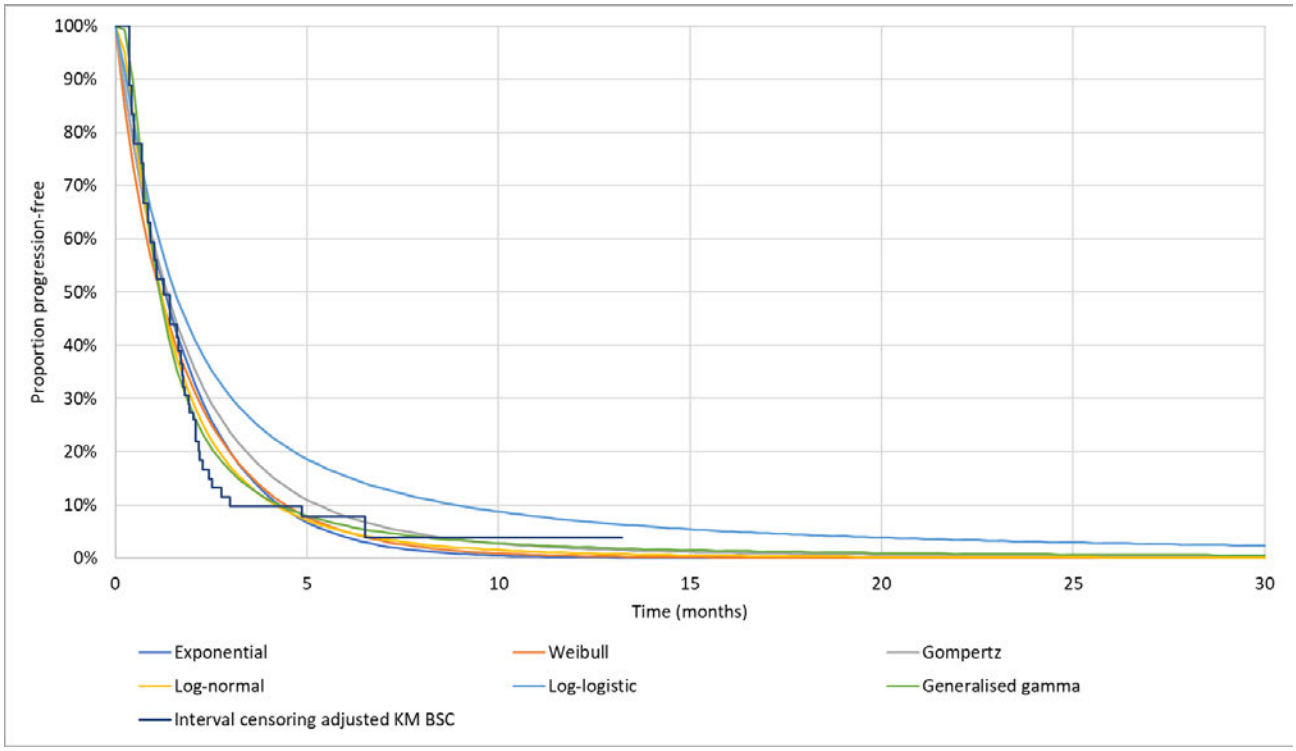
Whenever the PFS KM data is used directly in the model, the uncertainty around the KM is captured within sensitivity analyses by the Greenwood methods.

Figure 9 - Lonsurf interval censoring-adjusted PSM / curve fits and KM – PFS



Key: KM, Kaplan–Meier; PFS, progression-free survival; PSM, parametric survival model

Figure 10 - BSC interval censoring-adjusted PSM / curve fits and KM – PFS



Key: BSC, best supportive care; KM, Kaplan–Meier; PFS, progression-free survival; PSM, parametric survival model

Table 9 - Lonsurf and BSC statistical fit parameters – PFS

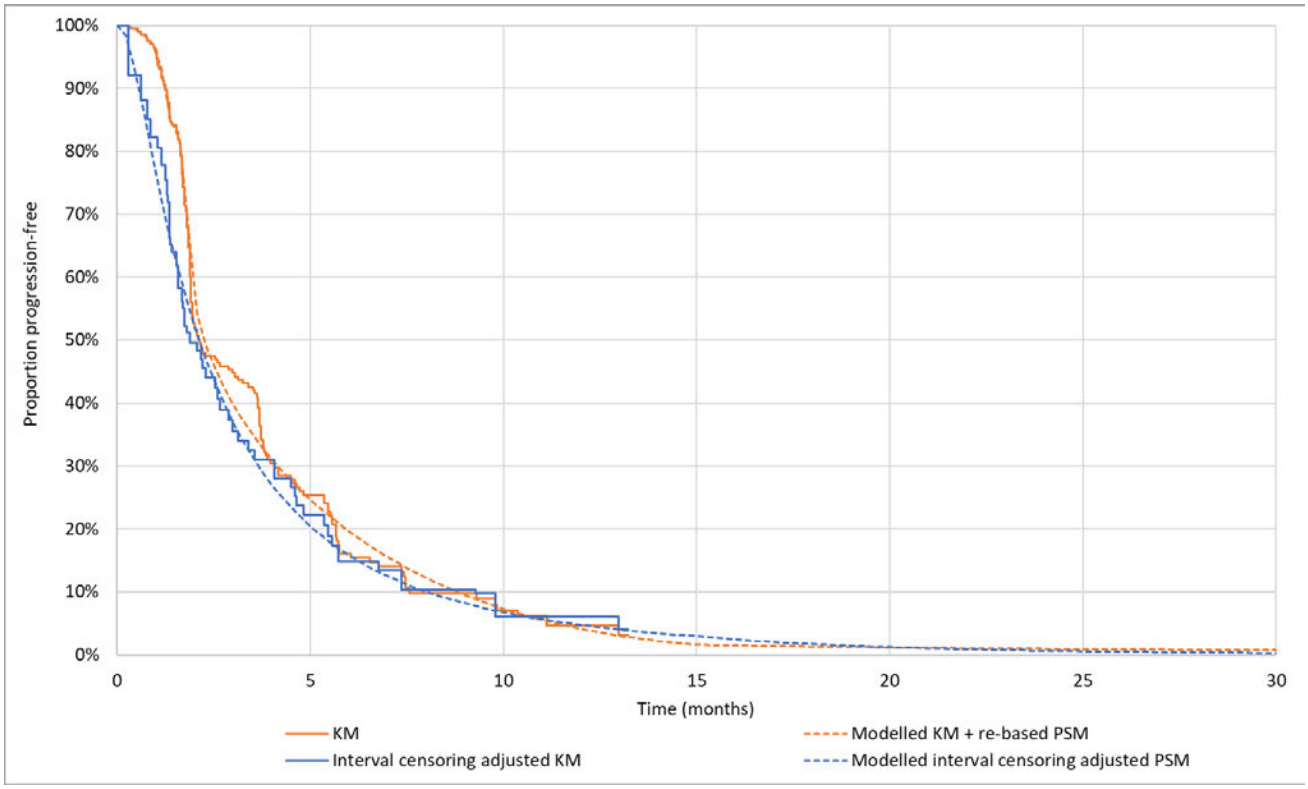
	Lonsurf		BSC	
Model	**AIC**	**BIC**	**AIC**	**BIC**
PSM				
Exponential	807.7157	811.0676	385.4903	388.1999
Weibull	784.8935	791.5972	369.5395	374.9586
Gompertz	806.8156	813.5193	387.2368	392.6558
Log-normal	741.8512	748.5549	333.3709	338.7900
Log-logistic	745.6287	752.3324	319.9901	325.4091
Generalised gamma	736.4144	746.4700	332.8652	340.9938
Re-based PSM				
Exponential	448.7118	451.6021	147.8032	149.8463
Weibull	405.6337	411.4144	83.5251	87.6112
Gompertz	444.1927	449.9734	107.6036	111.6897
Log-normal	431.1469	436.9276	79.8665	83.9526
Log-logistic	425.4841	431.2648	80.0469	84.1330
Generalised gamma	398.7289	407.4000	81.6895	87.8186
Interval censoring-adjusted PSM				
Exponential	633.2003	636.5522	265.4873	268.1968
Weibull	635.0304	641.7341	265.8914	271.3104
Gompertz	635.9166	642.6203	261.6635	267.0825
Log-normal	624.8051	631.5088	252.9317	258.3508
Log-logistic	653.2421	659.9458	266.6062	272.0252
Generalised gamma	626.0947	636.1503	251.3780	259.5066

Key: AIC, Akaike information criteria; BIC, Bayesian information criterion; BSC, best supportive care; PFS, progression-free survival; PSM, parametric survival model.

Table 10 - Lonsurf and BSC – median and mean PFS

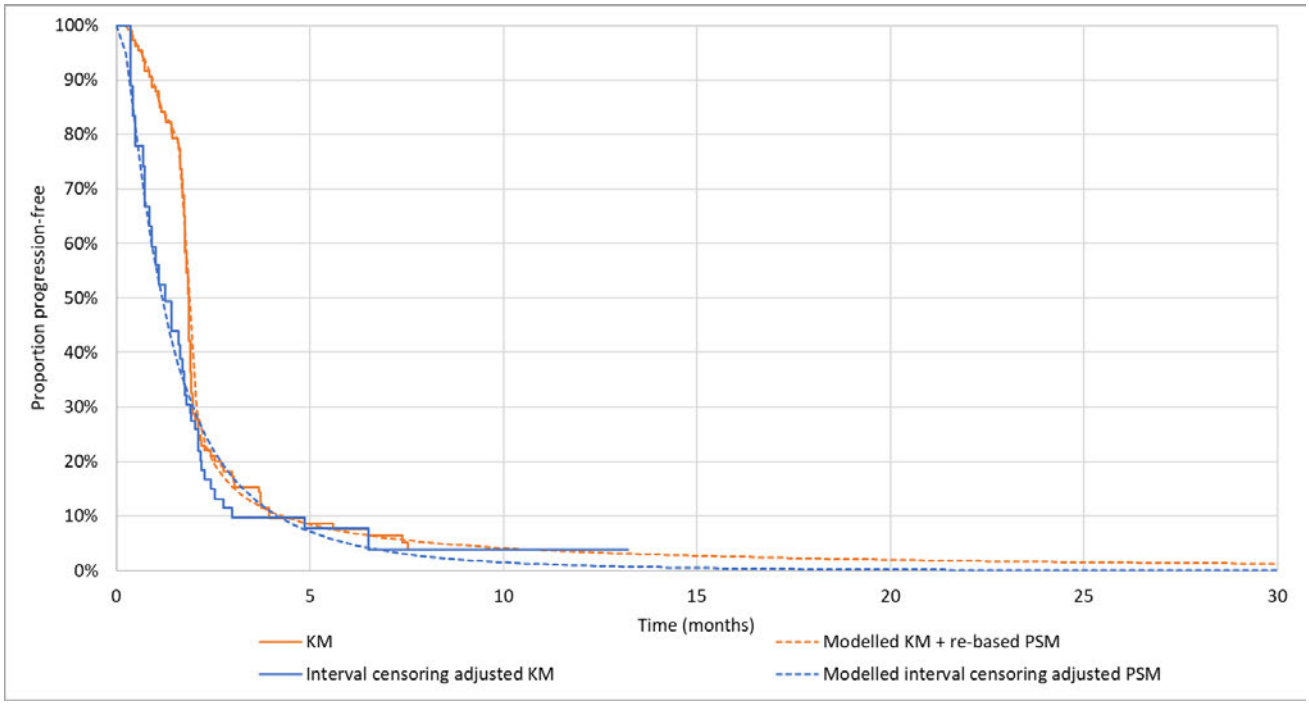
	Median PFS (months)		Mean PFS (months)	
Model	**Lonsurf**	**BSC**	**Lonsurf**	**BSC**
PSM				
Exponential	2.5	1.4	3.5	2.2
Weibull	2.8	1.8	3.4	2.1
Gompertz	2.8	1.6	3.4	2.1
Log-normal	2.5	1.6	3.4	2.1
Log-logistic	2.5	1.6	3.3	1.9
Generalised gamma	2.5	1.6	3.6	2.1
KM + PSM				
Exponential	1.8	1.6	3.6	2.1
Weibull	1.8	1.6	3.3	1.9
Gompertz	1.8	1.6	3.4	2.0
Log-normal	1.8	1.6	3.5	1.9
Log-logistic	1.8	1.6	3.7	1.8
Generalised gamma	1.8	1.6	3.8	1.9
Key: BSC, best supportive care; OS, overall survival; PSM, parametric survival model.				

Figure 11 - Lonsurf re-based PSM vs. interval censoring-adjusted PSM / best fitting curves and corresponding KM – PFS



Key: KM, Kaplan–Meier; PFS, progression-free survival; PSM, parametric survival model

Figure 12 - BSC re-based PSM vs. interval censoring-adjusted PSM / best fitting curves and corresponding KM – PFS



Key: BSC, best supportive care; KM, Kaplan–Meier; PFS, progression-free survival; PSM, parametric survival model

Treatment effect duration

A maximum treatment effect duration can be applied to Lonsurf's PFS. This means that from a user-amendable time point, it is assumed that there is no longer a treatment effect for Lonsurf and the probability of progression for Lonsurf is therefore the same as in the BSC arm. The base case model includes this treatment effect duration cap, as it reflects a more conservative approach to Lonsurf's treatment effect duration. The base case model uses a cut-off time point of 15 months because it is known from the 'ROW, no prior ramucirumab' subgroup PFS KM data that there is an observed treatment effect for Lonsurf versus BSC until approximately 14 months, and it is reasonable to assume that this treatment effect continues for a little longer.

In the model, the user can apply the treatment effect duration cap to any of the PFS PSM options. This is achieved in the model by applying the conditional PFS of the modelled BSC PFS curve to the modelled Lonsurf PFS curve, from 15 months onwards.

6.2.1.4 Time on treatment

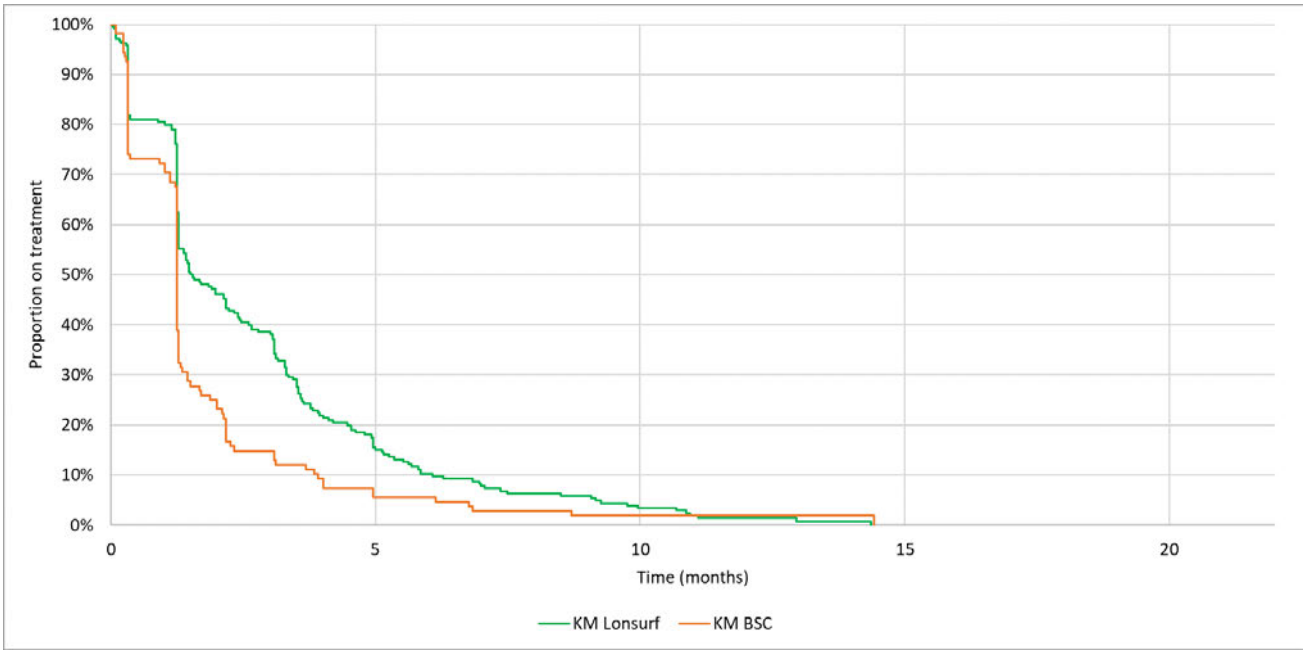
ToT is derived using the treatment start date (TRTSDT) and the treatment end date (TRTEDT) variables reported in the time-to-event dataset (ADTTE). The equation used to calculate ToT is:

$$(TRTEDT - TRTSDT) + 1.$$

If a patient's treatment end date was before the data cut-off of 31 March 2018, the value of ToT was considered as an event. Patients with a treatment end date that was either missing or later than the

data cut-off date were censored. Figure 13 presents the ToT KM of the 'ROW, no prior ramucirumab' population for Lonsurf and BSC, as observed in the TAS-102-302 TAGS trial.

Figure 13 - Lonsurf and BSC KM - ToT

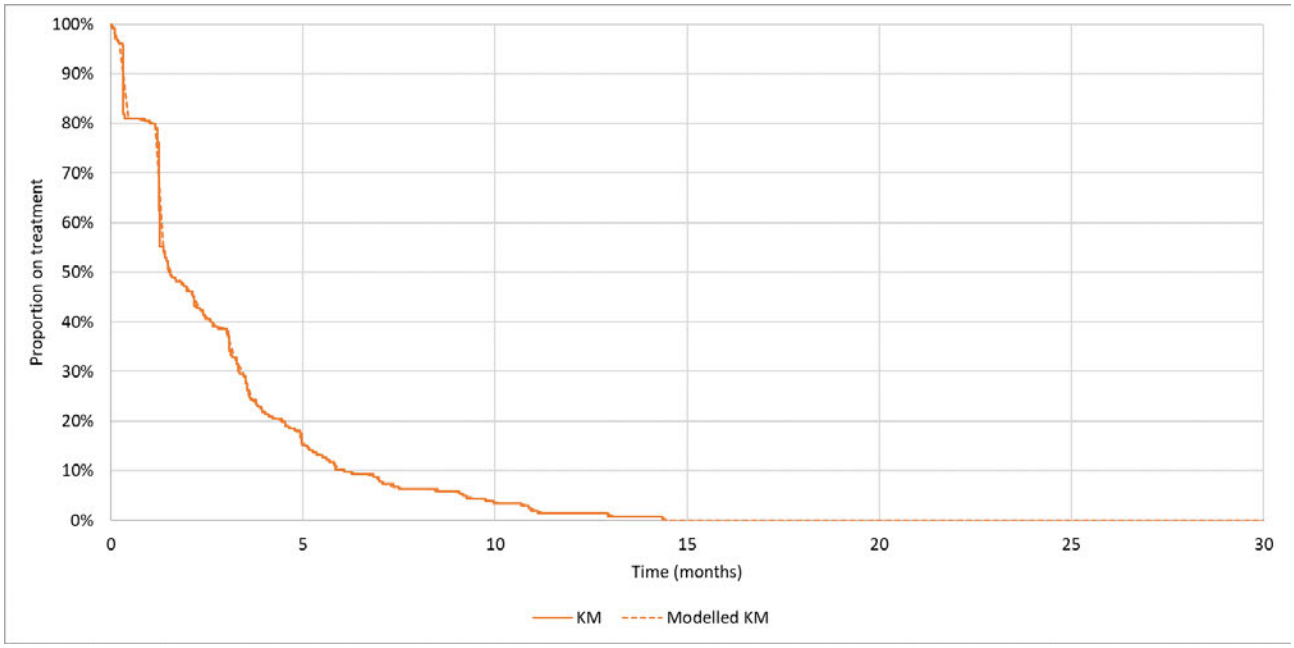


Time (months)	0	5	10
N at risk: Lonsurf	210	31	7
N at risk: Placebo	108	6	2

Key: BSC, best supportive care; KM; Kaplan–Meier; N, number; ToT, time on treatment

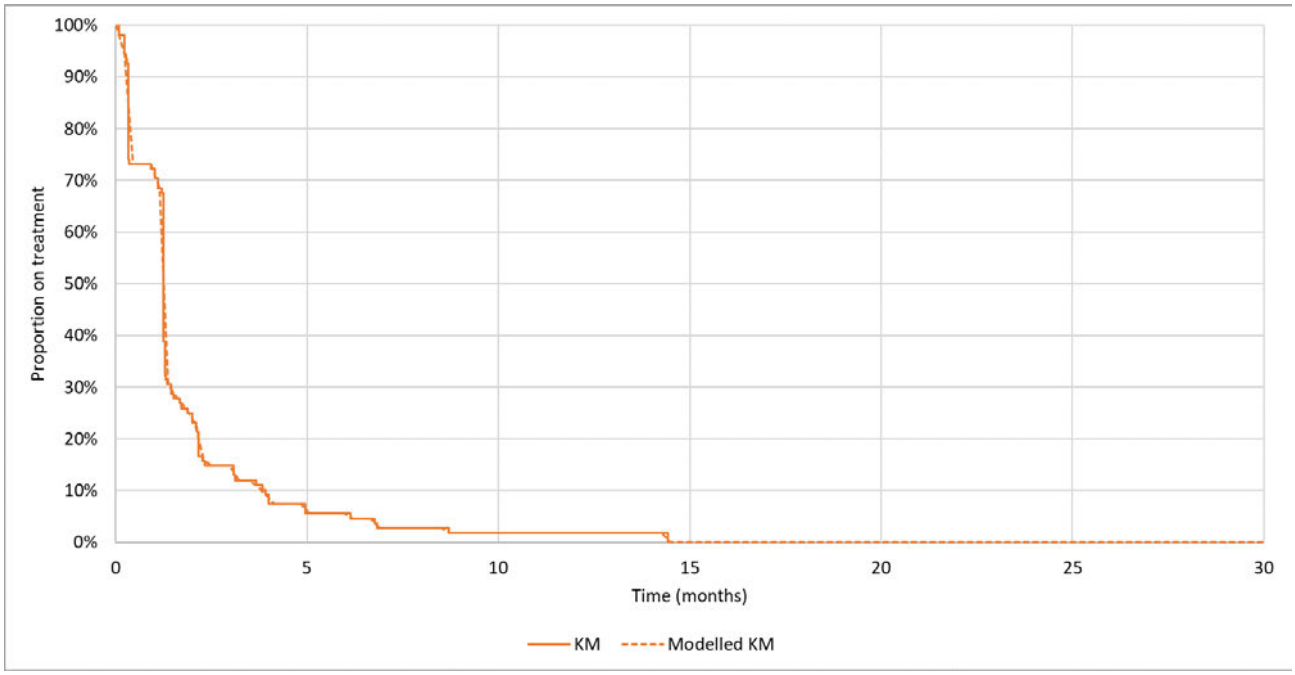
Since the ToT data are fully mature, the ToT KM data are used to model ToT in the Excel model and in the base case analysis. Figure 14 and Figure 15 show how the modelled ToT KM follows the observed ToT KM data of Lonsurf and BSC. The uncertainty around the ToT KM is captured within sensitivity analyses by the Greenwood methods.

Figure 14 - Lonsurf / modelled and observed KM - ToT



Key: ToT, time on treatment

Figure 15 - BSC / modelled and observed KM - ToT



Key: BSC, best supportive care; ToT, time on treatment

For completeness and to be consistent with the methods included to model PFS, the model also includes three additional options to model ToT:

- PSM
- KM + PSM
- KM + re-based PSM

As with the modelling of PFS, a cut-off point of 20% of patients still on treatment is used as the default setting in the option using KM + PSM. For the piecewise modelling option using KM + re-based PSM, the KM is used until 8 weeks, and PSM curves are fitted to the rest of the data. The six-stratified normal and re-based parametric curve fits to the ToT KM data. The interval censoring adjustment method is not used to model ToT, because there is no issue that patients may have stopped treatment at some unknown time between the previous assessment and the assessment that treatment is stopped. Table 11 presents the mean and median ToT estimate for all options included to model ToT.

The model also has the functionality to use data from the TAS-102-302 TAGS trial clinical study report (CSR) on the number of treatment cycles initiated in each of the treatment arms. By considering Lonsurf's treatment cycle length of 28 days, the number of treatment cycles is used to calculate a mean ToT. The mean values for number of treatment cycles of Lonsurf and BSC initiated in all four subgroups are presented in Table 12. As the CSR only gives the mean number of treatment cycles for the ITT and ROW populations, the 'ITT, no prior ramucirumab' population uses the ITT data as a placeholder; similarly, the 'ROW, no prior ramucirumab' population uses the ROW data as a placeholder. Comparing the mean ToT from the ToT KM with the mean ToT based on treatment cycles initiated for the base case subgroup shows that the mean ToT is quite similar between the two approaches. The mean ToT based on mean number of treatment cycles initiated is slightly higher as it only considers treatment cycles initiated, not whether these are completed.

Table 11 - Lonsurf and BSC – median and mean ToT

	Median ToT (months)		Mean ToT (months)	
Model	**Lonsurf**	**BSC**	**Lonsurf**	**BSC**
KM				
KM	1.4	1.1	2.9	1.9
PSM				
Exponential	1.8	1.1	2.9	1.9
Weibull	1.8	1.1	2.9	1.9
Gompertz	1.8	0.9	2.9	2.0
Log-normal	1.6	0.9	3.3	1.9
Log-logistic	1.6	0.9	3.8	2.1
Generalised gamma	1.8	0.9	2.9	1.9
KM + PSM				
Exponential	1.4	1.1	2.9	1.7
Weibull	1.4	1.1	2.9	1.7
Gompertz	1.4	1.1	2.9	1.7
Log-normal	1.4	1.1	3.5	1.7
Log-logistic	1.4	1.1	3.9	2.0
Generalised gamma	1.4	1.1	2.9	1.9
KM + re-based PSM				
Exponential	1.4	1.1	2.9	1.9
Weibull	1.4	1.1	2.9	1.9
Gompertz	1.4	1.1	2.9	2.1
Log-normal	1.4	1.1	5.2	2.1
Log-logistic	1.4	1.1	3.9	2.2
Generalised gamma	1.4	1.1	2.9	2.0

Key: BSC, best supportive care; KM, Kaplan–Meier; PSM, parametric survival model; ToT; time on treatment

Table 12 - Lonsurf and BSC – mean number of treatment cycles initiated

	Lonsurf			BSC			Reference
	Mean treatment cycles (N)	**SD**	**Mean ToT (months)**	**Mean treatment cycles (N)**	**SD**	**Mean ToT (months)**	
ITT	3.3	2.5	3.0	2.3	1.9	2.1	TAS-102-302 TAGS CSR
ROW	3.3	2.5	3.0	2.5	2.1	2.3	TAS-102-302 TAGS CSR
ITT, no prior ramucirumab	3.3	2.5	3.0	2.3	1.9	2.1	Placeholder data from ITT population
ROW, no prior ramucirumab	3.3	2.5	3.0	2.5	2.1	2.3	Placeholder data from ROW population
Key: BSC, best supportive care; CSR, clinical study report; ITT, intention to treat; N, number; ROW, rest of world, SD, standard deviation; ToT, time on treatment							

7. Resource consumption/quantities and costs

The following tables (from Table 13 to Table 19) depict the main costs outlined in the cost-effectiveness model.

Table 13 - Drug acquisition unit costs

Drug	**Dose**	**Number of Tablets**	**Price AIP**	**Reference**
Lonsurf	15mg	20	DKK 6135,52	SERVIER DK Price
		60	DKK 18398,65	
	20mg	20	DKK 8180,72	
		60	DKK 24534,19	
BSC				No cost
Key: BSC, best supportive care				

For the Danish submission the drug acquisition costs are set to the current SERVIER DK price AIP. The model has the functionality to use one out of three methods to deal with wastage:

1. No wastage essentially implies that patients share tablets. This is a hypothetical scenario that can be used to determine a lower bound for the drug acquisition costs for Lonsurf per patient
2. Pack sharing, no tablet sharing implies that patients can share packs of tablets, but no tablets
3. No pack sharing, no tablet sharing implies that patients cannot share tablets, nor packs of tablets

For the Danish submission the model has been set to “No pack sharing, no tablet sharing".

Missed doses and dose reductions as observed in the TAS-102-302 TAGS trial are considered in Lonsurf's relative dose intensity of 0.847. This relative dose intensity equals the ratio of the dose actually administered to the planned dose. Including relative dose intensity in the model implies that Lonsurf's drug acquisition costs are multiplied by 0.847. The model has the functionality to include or exclude relative dose intensity in the calculation of drug acquisition costs. The base case analysis includes relative dose intensity, as this leads to a more accurate estimation of drug acquisition costs.

The model includes a one-time cost equal to one nurse hour to account for the time required to instruct the patients how to take Lonsurf.

Table 14 - Drug administration unit costs

Drug administration costs component	Unit cost	Reference
Lonsurf administration	DKK 554.00	1 nurse hour. “Medicinraadet Værdisætning af enhedsomkostninger 2020"

Table 15 - Unit costs for AEs

Adverse event	Costs	Source: Danske DRG takster 2021
Anaemia	DKK 485.12	16PR01
Neutropenia	DKK 2,252.89	16MA03
Leukopenia	DKK 3,184.37	16MA03
Abdominal pain	DKK 11,394.50	06MA14
Ascites	DKK 5,697.25	06MA14
Fatigue	DKK 523.13	23MA05
Asthenia	DKK 334.22	23MA05
General physical health deterioration	DKK 5,742.55	23MA05
Neutrophil count decreased	DKK 1,867.53	16MA03
Decreased appetite	DKK 2,281.93	23MA05

In order to align the adverse events (AE) unit costs to the Danish diagnosis related group (DRG) costs a fundamentally different approach was taken for the Danish model. In the original model costs are based on AE Grade ≥ 3. However, since only a patient who experiences a serious AE is likely to incur a hospitalization cost, the definition of a serious AE in the trial was:

- Resulted in death;
- Was life-threatening, defined as an event in which the patient was at risk of death at the time of the event; it did not refer to an event which hypothetically might have caused death if it were more severe. May or may not have resulted in hospitalisation costs. However, to be conservative it is assumed that all these events will result in a DRG cost;
- Required in-patient hospitalization or prolongation of existing hospitalization. For these events the relevant DRG is applied, which in the case of prolonged hospitalisation could overestimate the actual costs.
- Resulted in persistent or significant disability/incapacity. May or may not have resulted in a hospitalization. However, to be conservative it is assumed that all these events will result in a DRG cost;
- Was a congenital anomaly or birth defect - not applicable for the TAGS study;
- Other important medical events that were not immediately life-threatening or resulted in death or hospitalization but jeopardized the patient or required intervention to prevent one of the other

outcomes listed above. Examples of such events were intensive treatment in an emergency room for allergic bronchospasm; blood dyscrasias or convulsions that did not result in hospitalization; or development of drug dependency or drug abuse. May or may not have resulted in a hospitalization. However, to be conservative it is assumed that all these events will result in a DRG cost.

The proportion of proportion of TEAE ≥ 3 is calculated based on the CSR supporting tables, Table 16[13].

Table 16 - TAEA Grade ≥3 included in the cost-effectiveness model[13]

AE in model	Table 14.3.2.1 TEAE Grade ≥3	Table 14.3.2.1 Serious TEAE Grade ≥3	Proportion of TEAE Grade ≥3 that are serious
Anaemia	137	11	0.08
Neutropenia	63	4	0.06
Leukopenia	78	7	0.09
Abdominal pain	14	7	0.50
Ascites	12	3	0.25
Fatigue	23	2	0.09
Asthenia	18	1	0.06
General physical health deterioration	22	21	0.95
Neutrophil count decreased	38	2	0.05
Decreased appetite	29	11	0.38

Key: AE, Adverse events; TEAE, Treatment emergent adverse events

Some patients in the TAS-102-302 TAGS trial received subsequent treatment. The model applies the total costs of these subsequent treatments as "Subsequent treatment costs". It was assumed that patients who had surgery only had one episode and the DRG 06MP13 was considered a reasonable medium level DRG to use. The purpose of palliative care is to improve through clinical intervention patients' general condition, increase quality of life and prolong life expectancy.

According to the Danish guidelines the methods used are surgical bypass, palliative resections or endoscopic modalities (tumor destruction using radiation therapy, thermal methods, photodynamic methods or internal by-passes in the form of stents). Furthermore, palliative oncology treatment can be offered a majority of patients.

Bypass of the outlet part of the ventricle is performed by transposition of the jejunum (GEA, gastroenteroanastomosis). The morbidity is high in these procedures (early complication rate 7-8%, late complication rate 18%). The initial success is the same for stents as for GEA (96%), just as lying days are the same. There is a higher recurrence rate of obstructive symptoms in stents just as these

patients have a shorter lifespan (Ia). In the long run, it has been shown that gastrointestinal by-pass has fewer complications and a better effect on the obstruction. Therefore, stents are only applied to patients with a short life expectancy (less than 2 months)[20]. For patients who receive radio-therapy the cost was assumed to consist of the planning DRG and the DRG for 3-4 radiation treatments. For simple chemotherapies it is assumed that the patient will be treated with docetaxel and patients treated with ramucirumab is assumed to be treated in combination with paclitaxel.

The unit costs of subsequent treatment are available in Table 17 and this same table also included the distribution of patients according to the subsequent treatment pathway, based on data collected from the TAGS clinical trial study[7].

Table 17 - Distribution of patients by subsequent treatment, by treatment arm and corresponding unit costs

Subsequent treatment	**Trifluridine/tipiracil (n=337), n (%)**	**Placebo (n=170), n (%)**	**Unit cost (per treatment cycle)**	**Reference**
Surgery	47 (13.9)	28 (16.5)	DKK 73,494.00	06MP13, Danske DRG takster 2021
Radiotherapy	8 (2.4)	5 (2.9)	DKK 7,694.00	27MP15, Danske DRG takster 2021 (Radiation Planning)
			DKK 34,770.00	27MP06, Danske DRG takster2021 (3-4 radiation treatments)
Standard chemotherapy	72 (21.4)	41 (24.1)	DKK 10,024.37	Calculated based on drug and administration cost as detailed in the model sheet: Subsequent treatment costs
Ramucirumab combination therapy	11 (3.3)	4 (2.4)	DKK 78,193.80	Calculated based on drug and administration cost as detailed in the model sheet: Subsequent treatment costs

Monitoring costs are separated into on-treatment and off-treatment monitoring costs. Patients on Lonsurf treatment follow the on-treatment monitoring costs, until treatment discontinuation and are assigned the off-treatment monitoring costs after that. Patients on BSC follow the off-treatment monitoring costs, as BSC is assumed to be equivalent to no active treatment.

Resource use is based on TA378[17] for ramucirumab in mGC and TA405[18] for Lonsurf in mCRC. Lonsurf is an oral drug, while ramucirumab is delivered via infusion, and therefore the frequency of consultant visits mentioned in TA405 for Lonsurf in mCRC is assumed to better reflect the clinical practice of Lonsurf. The frequency of computed tomography (CT) scans is derived from TA378 instead of from the CSR, because it is assumed that the frequency of visits given in TA378 better reflects clinical practice. The rates of full blood count, renal function and hepatic function tests are also derived from TA378. Renal function and hepatic function tests are applicable for Lonsurf as patients should be monitored on renal or hepatic impairment during active treatment with Lonsurf. It is also indicated in the SmPC that a doctor will perform blood tests before each treatment cycle of Lonsurf. The cost of a full blood count per treatment cycle is therefore also considered. The off-treatment resource use only includes consultation visits every 12 weeks.

For both on-treatment and off-treatment monitoring resource use, the model includes the functionality to add the frequency of health home visitors, general practitioner (GP) home consultation, GP surgery visit, community nurse specialist visit, and district nurse visits.

Table 18 - Monitoring unit costs

Monitoring costs component	**Frequency**	**Unit cost**	**Reference**
Consultant visit on treatment	Once per cycle	DKK 658.00	Overlaege ½ time. "Medicinraadet Værdisætning af enhedsomkostninger 2020"
Consultant visit off treatment	Twice (end of treatment and 30-days after end of treatment)	DKK 658.00	
CT scan	Every 8 weeks	DKK 2,007.00	30PR06, Danske DRG takster 2021
Full blood count	Once per cycle	DKK 129.00	Based on Prisliste for rutineanalyser KBA Bispebjerg Hospital;2021 2021-02-06. Cost of blood draw was estimated to be 100 DKK and proportioned equally across the 3 tests based on correspondence with Projekt Leder Mette Kongstad BBH
Renal function test	Once per cycle	DKK 114.00	
Hepatic function test	Once per cycle	DKK 62.00	
Key: CT, computed tomography			

Table 19 - End-of-life care costs

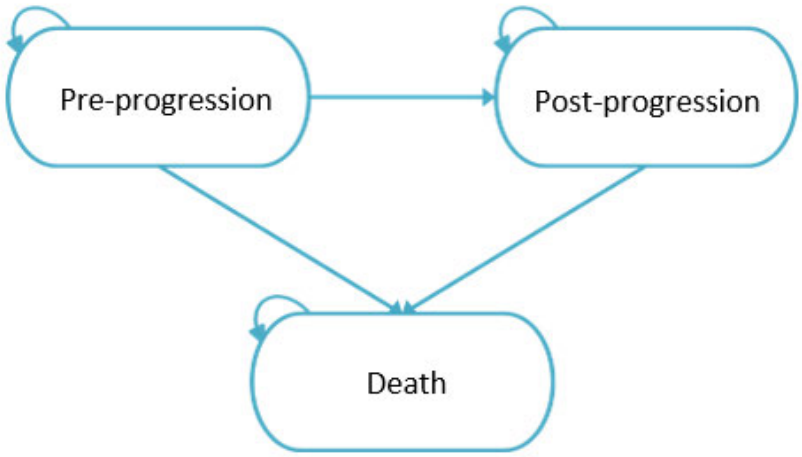
Source	**Unit cost**	**Reference**
User input*	DKK 88,471.00	DRG 26MP45, Danske DRG takster 2021
Key: N/A, not applicable.		

8. Methods and Results

8.1 Methods

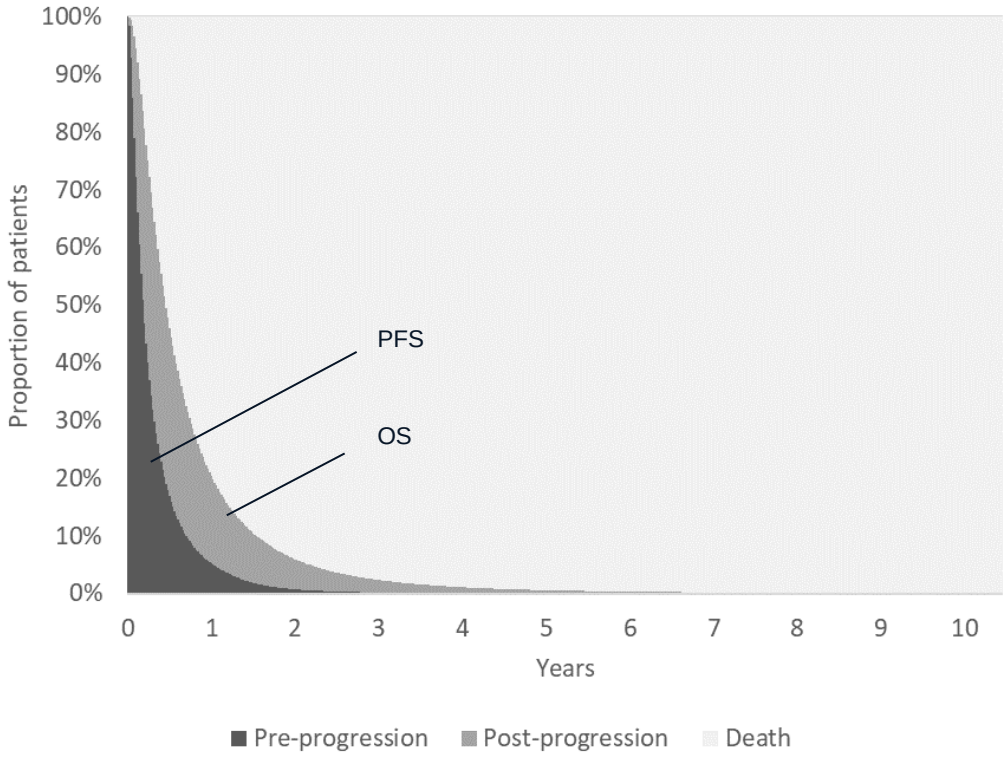
In brief the model is a trial based partitioned survival model. A partitioned survival (also known as an "area under the curve") cost-utility model was constructed in Microsoft Excel. A partitioned survival model calculates the proportion of patients by progression status (that is, those patients in pre- and post-progression) at a given time point based on survival curves and uses these proportions to inform the benefits accrued and costs incurred over the time horizon of the model. The model utilizes a standard 3-state structure of pre-progression survival, post-progression survival, and death. This structure was chosen based on its wide use health technology assessments in cancer. The model structure is presented in Figure 16.

Figure 16 - Health states in the partitioned survival model



Efficacy, resource use, and safety data for Lonsurf and BSC used in the model were derived from the pivotal phase III TAS-102-302 TAGS trial[7]. The key assumptions are presented in Table 20.

Figure 17 - Illustrative model structure



Key: OS, overall survival; PFS, progression-free survival

Table 20 - Key model assumptions

Assumptions	Base Case
Model Type	Partitioned Survival Model
Clinical data source	TAS-1-2-302 TAGS Study
Perspective	Hospital perspective
Time Horizon	10 years
Discount Rate	3.50%
Included Costs	Drug Adverse Events Disease Monitoring End of Life/Death
Dosing	Weight based dose banding
Treatment Line	3rd and later lines
Treatment Duration	Intervention: Until progression or treatment limiting adverse event Comparitor: Until progression or treatment limiting adverse event
Subsequent Treatment	Subsequent cancer treatment
Distribution for Time on Treatment	Intervention: KM curves Comparitor: KM curves
Parametric distribution for PFS	Intervention: Log-normal Comparitor: Log-normal
Parametric distribution for OS	Intervention: Log-normal Comparitor: Log-normal
Including Waste	Yes

8.2 Uncertainty

The uncertainty in the estimated cost per patient of using Lonsurf *versus* BSC is assessed by a one-way sensitivity analysis (OWSA). In brief for parameters generated from the trial the standard deviation was used and for parameters such as costs the SE was assumed to be +/- 10% of the base case value. The detailed list of the parameters and the range used in the OWSA is show in Appendix 4 Parameter list used in the OWSA. Since the original BresMed Model was a cost-effectiveness model the model output for the OWSA was Net Monetary Benefit the results of the OWSA presented in based in the cost part of the original OWSA. The numbers used for this report are in column AK and AL line 66 to 88 in the sheet named OWSA.

8.3 Results

Based on the model the mean additional cost of treating a mGC patient in 3rd or later lines of therapy is DKK 84,428 (Table 21) of that DKK 73,147 (87%) is cost of drug.

Table 21 - Itemized average cost per treated patient

Cost Item	Lonsurf	BSC	Incremental
Drug acquisition costs	DKK 73,147	DKK 0	DKK 73,147
Drug administration costs	DKK 554	DKK 0	DKK 554
Adverse event costs	DKK 1,221	DKK 134	DKK 1,087

Monitoring costs on Treatment	DKK 5,066	DKK 409	DKK 4,658
Monitoring costs off Treatment	DKK 1,308	DKK 1,069	DKK 239
Subsequent treatment costs	DKK 26,722	DKK 27,378	-DKK 656
End of life costs	DKK 87,583	DKK 87,970	-DKK 386
Social Costs	DKK 21,829	DKK 16,045	DKK 5,785
Total	**DKK 217,431**	**DKK 133,004**	**DKK 84,428**

Due to the short life expectancy of patients with mGC, 89% (DKK 75,152) of the additional cost occurs in the first year and 96% of the total cost occurring before the end of the 2nd year (Table 22).

Table 22 - Additional mean cost per patient by year after treatment initiation

Year after treatment initiation	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 10**
Additional Cost	DKK 75,152	DKK 81,338	DKK 83,143	DKK 83,823	DKK 84,120	DKK 84,428
Percent of Max	89%	96%	98%	99%	100%	100%

The most influential factor that impacts the cost is the duration of treatment which in the OWSA results in a range of additional cost of treating with Lonsurf range from DKK 76,692 to DKK 94,522 per treatment (Table 23).

Table 23 - The range of the estimate of the cost of treating one patient with Lonsurf® versus best supportive care for the ten most important parameters from the one-way sensitivity analysis

Parameter	**High**	**Low**	**Difference**
ToT Lonsurf®	DKK 94,522	DKK 76,692	DKK 17,830
Subsequent treatment costs SACT ramucirumab duration (treatment cycles)	DKK 85,497	DKK 83,457	DKK 2,041

Subsequent treatment costs ramucirumab	DKK 85,497	DKK 83,457	DKK 2,041
BSC - Subsequent treatment proportion SACT ramucirumab	DKK 85,447	DKK 83,409	DKK 2,038
Costs CT scan	DKK 84,997	DKK 83,911	DKK 1,087
On treatment CT scan rate	DKK 84,970	DKK 83,885	DKK 1,085
Costs consultant visit on treatment	DKK 84,928	DKK 83,974	DKK 954
On treatment consultant visit rate	DKK 84,904	DKK 83,951	DKK 953
Subsequent treatment costs surgery duration (treatment cycles)	DKK 84,910	DKK 83,990	DKK 920
Subsequent treatment costs surgery	DKK 84,910	DKK 83,990	DKK 920

9. Discussion

The economic analysis of the cost impact of Lonsurf versus best supportive care in treatment of 3rd or later lines mGC is based on the efficacy, safety, adverse events, and resource use observed in the TAS-102-302 TAGS study when is administered according to the SmPC. The key assumption in the model is that the efficacy, resource use and safety observed in the trial are representative of the efficacy, resource use, and safety in routine medical care.

Based on the economic model it is estimated that the mean additional cost of adding Lonsurf to the treatment sequence is **DKK 84,428.**

Cost of Lonsurf is the major cost contributor accounting for 87% of the cost increase. Since there are neither other major cost contributor nor major medical cost off-set the primary driver of uncertainty in this estimate is the duration of treatment. In the TAS-102-302 TAGS trial the reason for discontinuation was in 57.3% of patients due to radiological progression, 16.1% due to clinical progression and adverse events in 9.9%[5] of cases. It cannot be excluded that in clinical practice fewer CT scans will be performed which could lead to slightly longer treatment time that what was observed in the TAS-102-302 TAGS trial.

10. Budget Impact

A simple standalone budget impact (BI) model has been developed to provide an initial approximation of the net costs to apply Lonsurf as a third-line treatment in mGC. The results of this model are estimates of the total costs excluding patient and caregiver cost in a scenario with trifluridine/tipiracil minus the total costs in a scenario without Lonsurf for the upcoming five years.

The 3L+ mGC eligible patient population (EPP) was estimated based on "Medicinrådets protokol for vurdering af trifluridin/tipiracil som monoterapi til behandling af voksne patienter med metastatisk kræft I mavesæk og mavemund (adenocarcinom) efter mindst to tidligere behandlinger for fremskreden sygdom"[19]. The Danish guidelines states that; "In case of progression on first-line treatment, patients in good general condition should be offered further systemic oncological treatment (evidence A).

- Irinotecan monotherapy (A)
- Docetaxel or paclitaxel monotherapy (A)
- Ramucirumab monotherapy (A)
- Ramucirumab in combination with paclitaxel (A)
- Trifluridine / tipiracil as 3rd line treatment (A)
- Pembrolizumab in patients with dMMR / MSI-H (B)

The EMA-approved indication for Lonsurf is patients who have received at least two prior systemic treatment regimens for advanced disease and are candidates for 3rd-line systemic treatment. Overall, the expert committee estimates that less than 50 patients annually will be candidates for Lonsurf and in our assumption we have overestimated the annual incidence to be 50 patients[19].

Table 24 - Eligible patient population for Lonsurf®

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated eligible patient population	50	50	50	50	50

Drug acquisition costs per year for Lonsurf and alternative treatments are calculated by the model based on the drug acquisition costs per month and the mean months on treatment. Mean on months on treatment for trifluridine/tipiracil is set at three months, which is derived from the TAS-102-302 TAGS trial.[7]

10.1 Budgetary consequences on the drug budget of the National Insurance Scheme

Number of patients

Lonsurf is the only treatment that demonstrates a statistically significant and clinically-meaningful OS benefit in a global Phase III trial in 3L+ mGC. Lonsurf plus BSC demonstrates a 31% reduction in the risk of death when directly compared to placebo plus BSC, which translates into nearly half of all patients being alive at 6 months (47% vs. 33%), and over 20% alive at 1 year (21% vs. 13%), in a rapidly progressing, lethal disease with poor prognosis and no indicated treatment options, while concurrently providing a manageable safety profile and maintaining patients' HR-QoL. From Medicinrådets protokol 98800: "Aktuelt findes ikke godkendte 3. linjebehandlinger med veldokumenteret effekt, og de fleste patienter overgår til palliativ behandling. Hos et fåtal af patienter kan der forsøges med systemisk, antineoplastisk behandling i 3. linje. Det sker ved sekventiel anvendelse af lægemidlerne fra 2. linje, dvs. disse kan anvendes hvis de ikke tidligere har været anvendt. Det skal dog understreges, at dette ikke kan betragtes, eller i praksis fungerer, som standardbehandling, da der ikke findes dokumentation for effekten af taxaner eller irinotecan efter 2. linje." In accordance with the above we assume, in table 25, that the market penetration will be rather fast with 40% of patients receiving treatment with Lonsurf in year 1. Since there are no approved alternatives of 3rd line treatments we have considered BSC (Best Supportive Care) as the comparator and the expected number of patients treated with BSC if Lonsurf is approved for reimbursement is 50 per year (Table 26).

Relevance of the documentation for Danish clinical practice: In Denmark there is currently no recommended third-line palliative chemotherapy for metastatic gastro-oesophageal cancer.

Table 25 - Number of patients that are expected to be treated over the next five-year period - if the pharmaceutical is approved for reimbursement (base case)

	Year 1	Year 2	Year 3	Year 4	Year 5
For the pharmaceutical under consideration	20	30	40	50	50
BSC*	30	20	10	0	0

*BSC = Best Supportive Care

Table 26 - Number of patients expected to be treated during the next five-year period - if the pharmaceutical is NOT approved for reimbursement

	Year 1	Year 2	Year 3	Year 4	Year 5
For the pharmaceutical under consideration	0	0	0	0	0
BSC*	50	50	50	50	50

*BSC = Best Supportive Care

Expenditure per patient

The expenditure per patients is calculated based on all costs except the patient and caregiver costs. The estimated cost of treating the patients based on the above-mentioned market penetration for the two scenarios of Lonsurf being approved for reimbursement and Lonsurf NOT being approved for reimbursement are presented in Table 27 and Table 28 respectively.

Table 27 - Healthcare expenditure in DKK per year - if the pharmaceutical is approved for reimbursement

Annual expenditure if Lonsurf is reimbursed	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
For the drug under consideration; expenditure if drug reimbursed	DKK 3,549,001	DKK 5,604,808	DKK 7,582,240	DKK 9,549,485	DKK 9,740,332
For best supportive care; expenditure if drug reimbursed	DKK 3,176,203	DKK 2,388,281	DKK 1,289,942	DKK 139,607	DKK 33,251
Total expenditure to both Lonsurf and BSC if the drug is reimbursed	DKK 6,725,205	DKK 7,993,089	DKK 8,872,182	DKK 9,689,092	DKK 9,773,583

Table 28 - Healthcare per year - if the pharmaceutical is NOT approved for reimbursement

Best supportive care, expenditure if drug not reimbursed	DKK 5,293,672	DKK 5,745,026	DKK 5,829,470	DKK 5,855,400	DKK 5,865,383

10.2 Budget Impact

If Lonsurf is approved for reimbursement and with the fairly aggressive assumption of a market penetration of 40% first year, 60% second year, 80% third year and all patient treated with Lonsurf in the 4 year the budget impact will increase from DKK 1,431,532 in year 1 to DKK 3,908,200 in year 5 (Table 29).

Table 29 - The expected budget impact in DKK of the pharmaceutical pre-approved for reimbursement at the current indication

Budget Impact	Year 1	Year 2	Year 3	Year 4	Year 5
Total cost of drug under consideration and BSC if reimbursed	DKK 6,725,205	DKK 7,993,089	DKK 8,872,182	DKK 9,689,092	DKK 9,773,583
Best supportive care if not reimbursed	DKK 5,293,672	DKK 5,745,026	DKK 5,829,470	DKK 5,855,400	DKK 5,865,383
Budget impact of the recommendation	**DKK 1,431,532**	**DKK 2,248,063**	**DKK 3,042,713**	**DKK 3,833,692**	**DKK 3,908,200**

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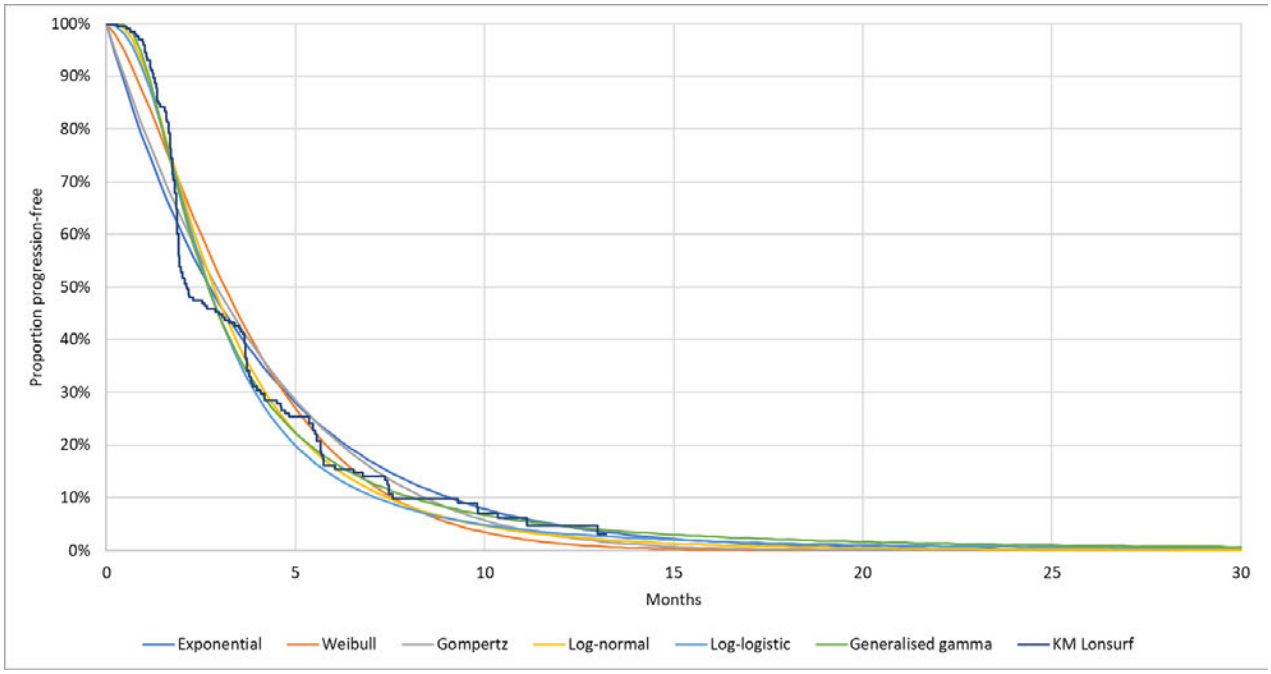
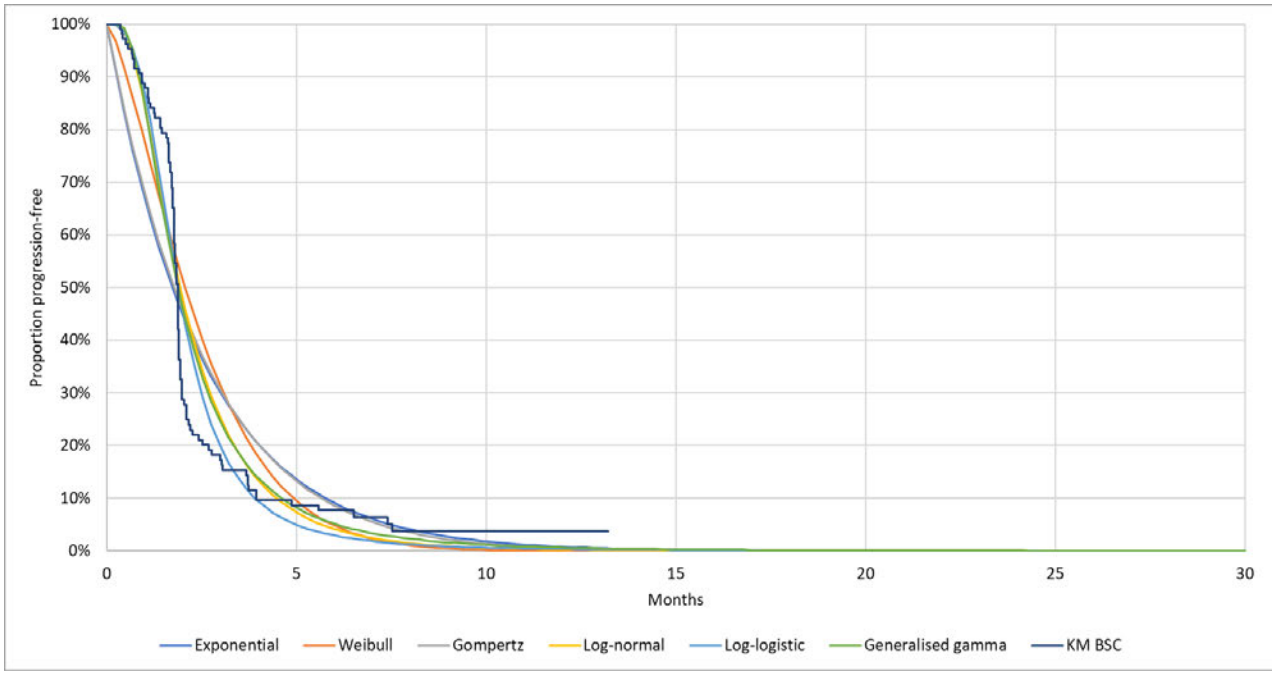
Appendix 1: Progression-free survival model methods

Lonsurf PSM / curve fits – PFS



Key: KM, Kaplan–Meier; PFS, progression-free survival; PSM, parametric survival model.

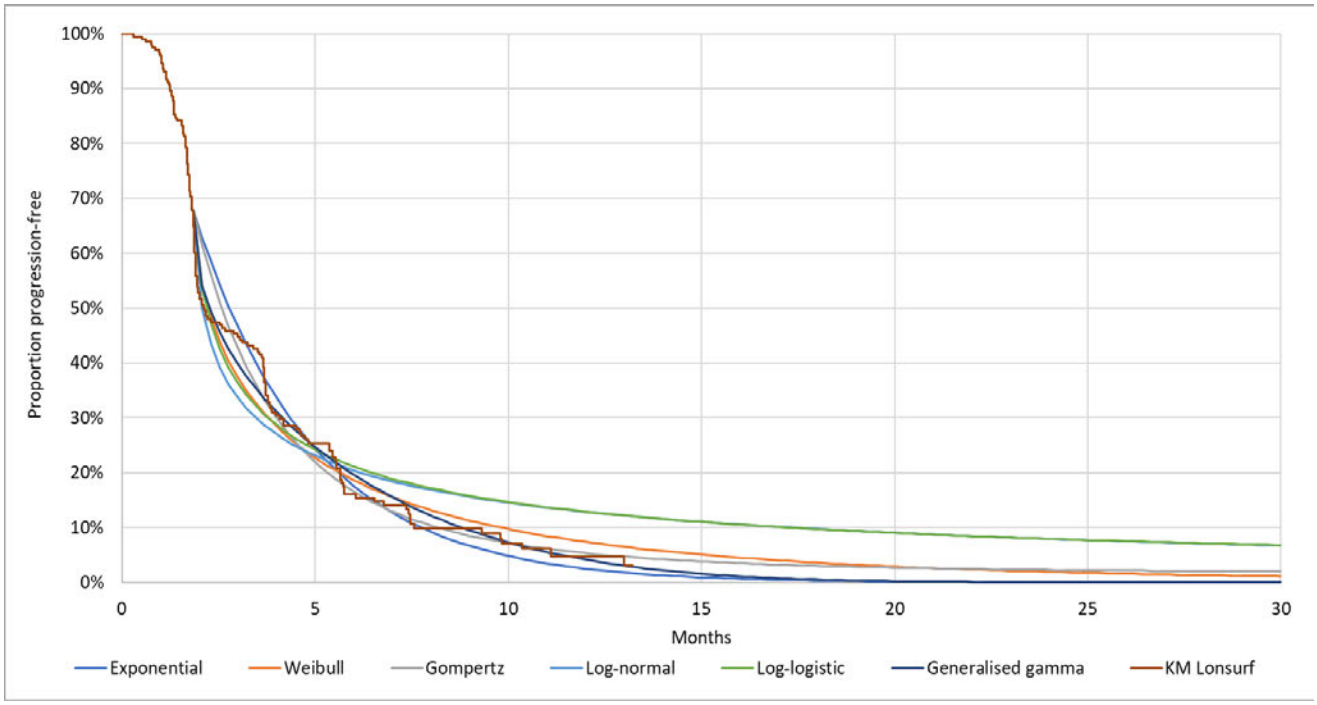
BSC PSM / curve fits – PFS



Key: BSC, best supportive care; KM, Kaplan–Meier; PFS, progression-free survival; PSM, parametric survival model.

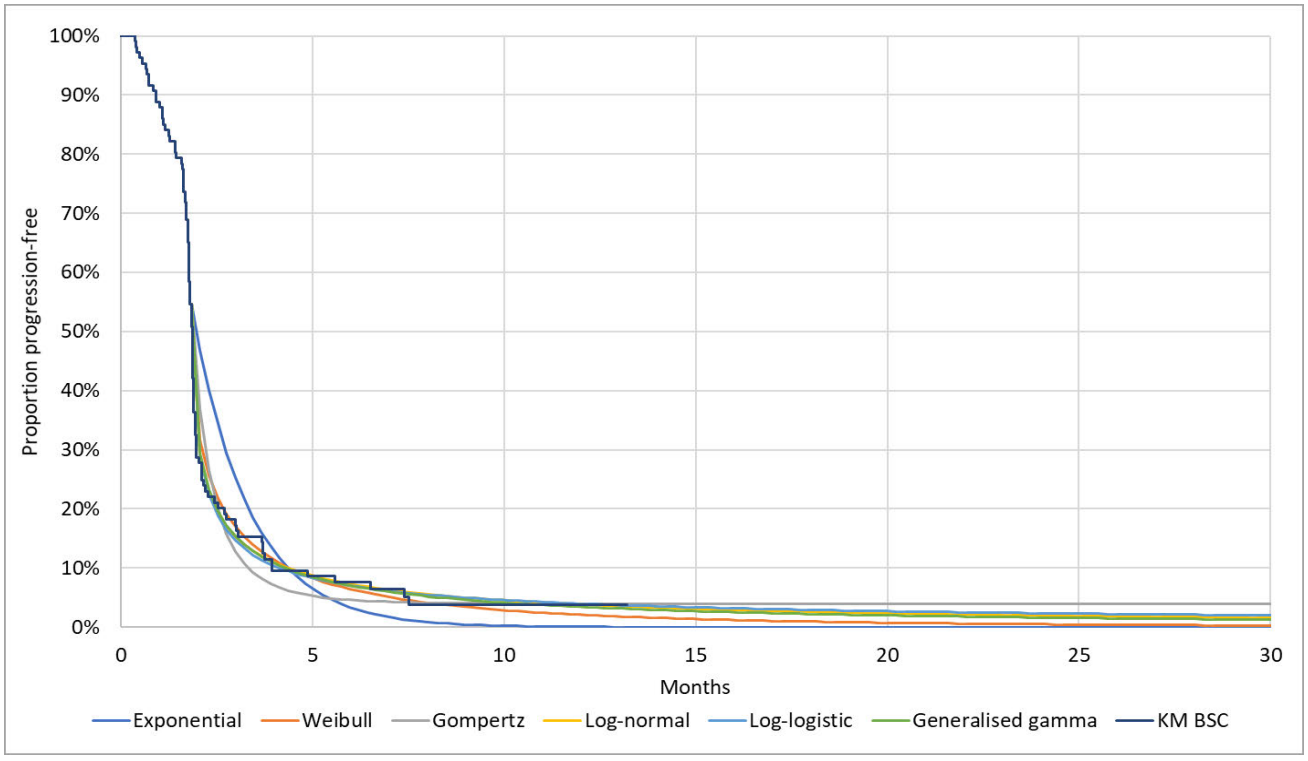
Appendix 2: KM + re-based PSM / curve fits

Lonsurf – PFS



Key: KM, Kaplan–Meier; PFS, progression-free survival; PSM, parametric survival model.

BSC – PFS



Key: BSC, best supportive care; KM, Kaplan–Meier; PFS, progression-free survival; PSM, parametric survival model.

Appendix 3: Lonsurf and BSC PSM / percentage of patients progression free at selected time horizons

	Time horizon (years)					
	Lonsurf			BSC		
Model	**1 year**	**2 years**	**3 years**	**1 year**	**2 years**	**3 years**
KM						
KM	5%	0%	0%	4%	0%	0%
PSM						
Exponential	5%	0%	0%	1%	0%	0%
Weibull	1%	0%	0%	0%	0%	0%
Gompertz	3%	0%	0%	1%	0%	0%
Log-normal	3%	0%	0%	0%	0%	0%
Log-logistic	3%	0%	0%	0%	0%	0%
Generalised gamma	5%	1%	0%	1%	0%	0%
KM + PSM						
Exponential	4%	0%	0%	0%	0%	0%
Weibull	1%	0%	0%	0%	0%	0%
Gompertz	3%	0%	0%	0%	0%	0%
Log-normal	3%	0%	0%	0%	0%	0%
Log-logistic	5%	1%	0%	0%	0%	0%
Generalised gamma	6%	1%	0%	0%	0%	0%
KM + re-based PSM						
Exponential	3%	0%	0%	0%	0%	0%
Weibull	7%	2%	1%	2%	0%	0%
Gompertz	5%	4%	2%	4%	3%	1%
Log-normal	13%	5%	2%	4%	2%	1%
Log-logistic	13%	5%	2%	4%	2%	1%
Generalised gamma	4%	1%	1%	3%	2%	1%
Interval censoring-adjusted PSM						
Exponential	3%	0%	0%	0%	0%	0%
Weibull	3%	0%	0%	0%	0%	0%
Gompertz	9%	4%	3%	2%	0%	0%
Log-normal	5%	1%	0%	1%	0%	0%
Log-logistic	16%	7%	4%	7%	3%	2%
Generalised gamma	6%	2%	1%	2%	1%	0%

Key: BSC, best supportive care; KM, Kaplan–Meier; PSM, parametric survival model.

Appendix 4 Parameter list used in the OWSA

Where no distribution data were known for a parameter, the standard error assumed plus or minus 10% of the mean for the calculation of upper and lower bounds.

Table 30: Parameter table

Parameter description	Mean/ Base value	Lower bound	Upper bound	Distribution
Controls				
Discount rate for life years	0%			
Discount rate for quality-adjusted life years	3.5%			
Discount rate for costs	3.5%			
PAS Lonsurf	20%			
Mean age	61.52	60.31	62.74	
Mean BSA	1.78	1.76	1.80	
Percentage of males	73%	73%	73%	

Parameter description	Mean/ Base value	Lower bound	Upper bound	Distribution
Time on treatment				
ToT- Lonsurf - mean number of treatment cycles from CSR	3.3	3.0	3.6	Gamma
ToT- BSC - mean number of treatment cycles from CSR	2.5	2.2	2.9	Gamma
ToT - Lonsurf - exponential curve fit - rate	-1.030			Multivariate normal
ToT - Lonsurf - exponential curve fit - treatment effect	0.000			Multivariate normal
ToT - Lonsurf - Weibull curve fit - shape	0.049			Multivariate normal
ToT - Lonsurf - Weibull curve fit - scale	1.049			Multivariate normal
ToT - Lonsurf - Weibull curve fit - treatment effect	0.000			Multivariate normal
ToT - Lonsurf - Gompertz curve fit - shape	0.004			Multivariate normal
ToT - Lonsurf - Gompertz curve fit - rate	-1.041			Multivariate normal
ToT - Lonsurf - Gompertz curve fit - treatment effect	0.000			Multivariate normal
ToT - Lonsurf - lognormal curve fit - meanlog	0.519			Multivariate normal
ToT - Lonsurf - lognormal curve fit - sdlog	0.128			Multivariate normal
ToT - Lonsurf - lognormal curve fit - treatment effect	0.000			Multivariate normal
ToT - Lonsurf - loglogistic curve fit - shape	0.446			Multivariate normal
ToT - Lonsurf - loglogistic curve fit - scale	0.593			Multivariate normal
ToT - Lonsurf - loglogistic curve fit - treatment effect	0.000			Multivariate normal
ToT - Lonsurf - generalised gamma curve fit - mu	0.903			Multivariate normal
ToT - Lonsurf - generalised gamma curve fit - sigma	0.004			Multivariate normal
ToT - Lonsurf - generalised gamma curve fit - Q	0.710			Multivariate normal
ToT - Lonsurf - generalised gamma curve fit - treatment effect	0.000			Multivariate normal
ToT - BSC - exponential curve fit - rate	-0.577			Multivariate normal
ToT - BSC - exponential curve fit - treatment effect	0.000			Multivariate normal
ToT - BSC - Weibull curve fit - shape	0.026			Multivariate normal

Parameter description	Mean/ Base value	Lower bound	Upper bound	Distribution
ToT - BSC - Weibull curve fit - scale	0.589			Multivariate normal
ToT - BSC - Weibull curve fit - treatment effect	0.000			Multivariate normal
ToT - BSC - Gompertz curve fit - shape	-0.083			Multivariate normal
ToT - BSC - Gompertz curve fit - rate	-0.420			Multivariate normal
ToT - BSC - Gompertz curve fit - treatment effect	0.000			Multivariate normal
ToT - BSC - lognormal curve fit - meanlog	0.102			Multivariate normal
ToT - BSC - lognormal curve fit - sdlog	-0.013			Multivariate normal
ToT - BSC - lognormal curve fit - treatment effect	0.000			Multivariate normal
ToT - BSC - loglogistic curve fit - shape	0.586			Multivariate normal
ToT - BSC - loglogistic curve fit - scale	0.131			Multivariate normal
ToT - BSC - loglogistic curve fit - treatment effect	0.000			Multivariate normal
ToT - BSC - generalised gamma curve fit - mu	0.113			Multivariate normal
ToT - BSC - generalised gamma curve fit - sigma	-0.013			Multivariate normal
ToT - BSC - generalised gamma curve fit - Q	0.024			Multivariate normal
ToT - BSC - generalised gamma curve fit - treatment effect	0.000			Multivariate normal
ToT SD: Lonsurf - Applied as HR to incorporate uncertainty of KM data	1.000	0.824	1.176	Normal
ToT SD: BSC - Applied as HR to incorporate uncertainty of KM data	1.000	0.765	1.235	Normal

Parameter description	Mean/ Base value	Lower bound	Upper bound	Distribution
Progression-free survival				
PFS - Lonsurf - exponential curve fit - rate	-1.195			Multivariate normal
PFS - Lonsurf - exponential curve fit - treatment effect	0.000			Multivariate normal
PFS - Lonsurf - Weibull curve fit - shape	-0.029			Multivariate normal
PFS - Lonsurf - Weibull curve fit - scale	1.188			Multivariate normal
PFS - Lonsurf - Weibull curve fit - treatment effect	0.000			Multivariate normal
PFS - Lonsurf - Gompertz curve fit - shape	-0.101			Multivariate normal
PFS - Lonsurf - Gompertz curve fit - rate	-1.047			Multivariate normal
PFS - Lonsurf - Gompertz curve fit - treatment effect	0.000			Multivariate normal
PFS - Lonsurf - lognormal curve fit - meanlog	0.752			Multivariate normal
PFS - Lonsurf - lognormal curve fit - sdlog	0.038			Multivariate normal
PFS - Lonsurf - lognormal curve fit - treatment effect	0.000			Multivariate normal
PFS - Lonsurf - loglogistic curve fit - shape	0.238			Multivariate normal
PFS - Lonsurf - loglogistic curve fit - scale	1.144			Multivariate normal
PFS - Lonsurf - loglogistic curve fit - treatment effect	0.000			Multivariate normal
PFS - Lonsurf - generalised gamma curve fit - mu	0.616			Multivariate normal
PFS - Lonsurf - generalised gamma curve fit - sigma	-0.009			Multivariate normal
PFS - Lonsurf - generalised gamma curve fit - Q	-0.341			Multivariate normal
PFS - Lonsurf - generalised gamma curve fit - treatment effect	0.000			Multivariate normal
PFS - BSC - exponential curve fit - rate	-0.618			Multivariate normal
PFS - BSC - exponential curve fit - treatment effect	0.000			Multivariate normal
PFS - BSC - Weibull curve fit - shape	-0.117			Multivariate normal
PFS - BSC - Weibull curve fit - scale	0.555			Multivariate normal
PFS - BSC - Weibull curve fit - treatment effect	0.000			Multivariate normal

Parameter description	Mean/ Base value	Lower bound	Upper bound	Distribution
PFS - BSC - Gompertz curve fit - shape	-0.092			Multivariate normal
PFS - BSC - Gompertz curve fit - rate	-0.597			Multivariate normal
PFS - BSC - Gompertz curve fit - treatment effect	0.000			Multivariate normal
PFS - BSC - lognormal curve fit - meanlog	0.159			Multivariate normal
PFS - BSC - lognormal curve fit - sdlog	-0.010			Multivariate normal
PFS - BSC - lognormal curve fit - treatment effect	0.000			Multivariate normal
PFS - BSC - loglogistic curve fit - shape	0.230			Multivariate normal
PFS - BSC - loglogistic curve fit - scale	0.439			Multivariate normal
PFS - BSC - loglogistic curve fit - treatment effect	0.000			Multivariate normal
PFS - BSC - generalised gamma curve fit - mu	-0.082			Multivariate normal
PFS - BSC - generalised gamma curve fit - sigma	-0.235			Multivariate normal
PFS - BSC - generalised gamma curve fit - Q	-0.766			Multivariate normal
PFS - BSC - generalised gamma curve fit - treatment effect	0.000			Multivariate normal
PFS SD: Lonsurf - Applied as HR to incorporate uncertainty of KM data	1.000	0.804	1.196	Normal
PFS SD: BSC - Applied as HR to incorporate uncertainty of KM data	1.000	0.745	1.255	Normal

Parameter description	Mean/ Base value	Lower bound	Upper bound	Distribution
Overall survival				
OS - Lonsurf - exponential curve fit - rate	-2.055			Multivariate normal
OS - Lonsurf - exponential curve fit - treatment effect	0.000			Multivariate normal
OS - Lonsurf - Weibull curve fit - shape	0.254			Multivariate normal
OS - Lonsurf - Weibull curve fit - scale	2.040			Multivariate normal
OS - Lonsurf - Weibull curve fit - treatment effect	0.000			Multivariate normal
OS - Lonsurf - Gompertz curve fit - shape	0.038			Multivariate normal
OS - Lonsurf - Gompertz curve fit - rate	-2.225			Multivariate normal
OS - Lonsurf - Gompertz curve fit - treatment effect	0.000			Multivariate normal
OS - Lonsurf - lognormal curve fit - meanlog	1.656			Multivariate normal
OS - Lonsurf - lognormal curve fit - sdlog	-0.052			Multivariate normal
OS - Lonsurf - lognormal curve fit - treatment effect	0.000			Multivariate normal
OS - Lonsurf - loglogistic curve fit - shape	0.577			Multivariate normal
OS - Lonsurf - loglogistic curve fit - scale	1.661			Multivariate normal
OS - Lonsurf - loglogistic curve fit - treatment effect	0.000			Multivariate normal
OS - Lonsurf - generalised gamma curve fit - mu	1.641			Multivariate normal
OS - Lonsurf - generalised gamma curve fit - sigma	-0.048			Multivariate normal
OS - Lonsurf - generalised gamma curve fit - Q	-0.037			Multivariate normal
OS - Lonsurf - generalised gamma curve fit - treatment effect	0.000			Multivariate normal
OS - BSC - exponential curve fit - rate	-1.725			Multivariate normal
OS - BSC - exponential curve fit - treatment effect	0.000			Multivariate normal
OS - BSC - Weibull curve fit - shape	0.117			Multivariate normal
OS - BSC - Weibull curve fit - scale	1.737			Multivariate normal
OS - BSC - Weibull curve fit - treatment effect	0.000			Multivariate normal

Parameter description	Mean/ Base value	Lower bound	Upper bound	Distribution
OS - BSC - Gompertz curve fit - shape	-0.019			Multivariate normal
OS - BSC - Gompertz curve fit - rate	-1.655			Multivariate normal
OS - BSC - Gompertz curve fit - treatment effect	0.000			Multivariate normal
OS - BSC - lognormal curve fit - meanlog	1.296			Multivariate normal
OS - BSC - lognormal curve fit - sdlog	-0.001			Multivariate normal
OS - BSC - lognormal curve fit - treatment effect	0.000			Multivariate normal
OS - BSC - loglogistic curve fit - shape	0.540			Multivariate normal
OS - BSC - loglogistic curve fit - scale	1.270			Multivariate normal
OS - BSC - loglogistic curve fit - treatment effect	0.000			Multivariate normal
OS - BSC - generalised gamma curve fit - mu	1.132			Multivariate normal
OS - BSC - generalised gamma curve fit - sigma	0.012			Multivariate normal
OS - BSC - generalised gamma curve fit - Q	-0.363			Multivariate normal
OS - BSC - generalised gamma curve fit - treatment effect	0.000			Multivariate normal
OS SD: Lonsurf - Applied as HR to incorporate uncertainty of KM data	1.000	0.784	1.216	Normal
OS SD: BSC - Applied as HR to incorporate uncertainty of KM data	1.000	0.745	1.255	Normal

Parameter description	Mean/ Base value	Lower bound	Upper bound	Distribution
Adverse events				
Anaemia probability Lonsurf	0.74%	0.60%	0.89%	Beta
Neutropenia probability Lonsurf	2.27%	1.84%	2.73%	Beta
Leukopenia probability Lonsurf	0.65%	0.53%	0.78%	Beta
Abdominal pain probability Lonsurf	0.03%	0.02%	0.03%	Beta
Ascites probability Lonsurf	0.00%	0.00%	0.00%	Beta
Fatigue probability Lonsurf	0.28%	0.23%	0.33%	Beta
Asthenia probability Lonsurf	0.08%	0.07%	0.10%	Beta
General physical health deterioration probability Lonsurf	0.03%	0.02%	0.03%	Beta
Neutrophil count decreased probability Lonsurf	0.48%	0.39%	0.57%	Beta
Decreased appetite probability Lonsurf	0.16%	0.13%	0.20%	Beta
Anaemia probability BSC	0.43%	0.35%	0.52%	Beta
Neutropenia probability BSC	0.00%	0.00%	0.00%	Beta
Leukopenia probability BSC	0.00%	0.00%	0.00%	Beta
Abdominal pain probability BSC	0.00%	0.00%	0.00%	Beta
Ascites probability BSC	0.00%	0.00%	0.00%	Beta
Fatigue probability BSC	0.00%	0.00%	0.00%	Beta
Asthenia probability BSC	0.00%	0.00%	0.00%	Beta
General physical health deterioration probability BSC	0.00%	0.00%	0.00%	Beta
Neutrophil count decreased probability BSC	-1.030			Multivariate normal
Decreased appetite probability BSC	0.000			Multivariate normal

Parameter description	Mean/ Base value	Lower bound	Upper bound	Distribution
Utilities				
Utility Kontodimopoulos baseline	0.705			
Utility Kontodimopoulos intercept	-0.010			Multivariate normal
Utility Kontodimopoulos baseline coefficient	0.798			Multivariate normal
Utility Kontodimopoulos pre-progression coefficient	0.108			Multivariate normal
Utility Longworth baseline	0.666			
Utility Longworth intercept	-0.152			Multivariate normal
Utility Longworth baseline coefficient	0.951			Multivariate normal
Utility Longworth pre-progression coefficient	0.130			Multivariate normal
Utility pre-progression from ramucirumab appraisal	0.737	0.719	0.754	Beta
Utility pre-progression from trastuzumab appraisal	0.729	0.708	0.750	Beta
Utility post-progression from ramucirumab appraisal	0.587	0.552	0.622	Beta
Utility post-progression from trastuzumab appraisal	0.577	0.498	0.654	Beta
Utility pre-progression user input	0.660	0.525	0.783	Beta
Utility post-progression user input	0.552	0.443	0.659	Beta

Parameter description	Mean/ Base value	Lower bound	Upper bound	Distribution
Adverse event disutilities				
Anaemia disutility	-0.115	-0.093	-0.140	Beta
Neutropenia disutility	-0.090	-0.063	-0.121	Beta
Leukopenia disutility	-0.090	-0.063	-0.121	Beta
Abdominal pain disutility	-0.069	-0.001	-0.257	Beta
Ascites disutility	0.000	0.000	0.000	Beta
Fatigue disutility	-0.119	-0.096	-0.143	Beta
Asthenia disutility	0.000	0.000	0.000	Beta
General physical health deterioration disutility	0.000	0.000	0.000	Beta
Neutrophil count decreased disutility	-0.090	-0.063	-0.121	Beta
Decreased appetite disutility	0.000	0.000	0.000	Beta
Anaemia mean duration	16	13	19	Gamma
Neutropenia mean duration	15	12	18	Gamma
Leukopenia mean duration	20	16	24	Gamma
Abdominal pain mean duration	17	14	20	Gamma
Ascites mean duration	20	16	24	Gamma
Fatigue mean duration	32	26	38	Gamma
Asthenia mean duration	20	16	24	Gamma
General physical health deterioration mean duration	20	16	24	Gamma
Neutrophil count decreased mean duration	15	12	18	Gamma
Decreased appetite mean duration	20	16	24	Gamma

Parameter description	Mean/ Base value	Lower bound	Upper bound	Distribution
Drug acquisition costs				
Costs Lonsurf pack 300 mg	500.00			
Costs Lonsurf pack 900 mg	1500.00			
Costs Lonsurf pack 400 mg	666.67			
Costs Lonsurf pack 1200 mg	2000.00			
Lonsurf dose per administration	35.000			
Lonsurf relative dose intensity	0.847			

Parameter description	Mean/ Base value	Lower bound	Upper bound	Distribution
Drug administration costs				
Costs oral administration	141	113	169	Gamma

Parameter description	Mean/ Base value	Lower bound	Upper bound	Distribution
Adverse event costs				
Anaemia unit costs	3202	2574	3830	Gamma
Neutropenia unit costs	121	97	145	Gamma
Leukopenia unit costs	3415	2746	4084	Gamma
Abdominal pain unit costs	645	519	771	Gamma
Ascites unit costs	162	130	194	Gamma
Fatigue unit costs	13	10	15	Gamma
Asthenia unit costs	162	130	194	Gamma
General physical health deterioration unit costs	162	130	194	Gamma
Neutrophil count decreased unit costs	121	97	145	Gamma
Decreased appetite unit costs	162	130	194	Gamma

Parameter description	Mean/ Base value	Lower bound	Upper bound	Distribution
Monitoring costs				
Costs consultant visit on treatment	173	139	207	Gamma
Costs consultant visit off treatment	173	139	207	Gamma
Costs CT scan	106	85	127	Gamma
Costs full blood count	3	2	4	Gamma
Costs renal function test	1	1	1	Gamma
Costs hepatic function test	1	1	1	Gamma
Costs health home visitor	42	34	51	Gamma
Costs GP home consultation	43	35	52	Gamma
Costs GP surgery visit	31	25	38	Gamma
Costs community nurse specialist visit	46	37	55	Gamma
Costs district nurse	42	34	51	Gamma
Off treatment consultant visit rate	0.083	0.068	0.100	Gamma
Off treatment CT scan rate	0.000	0.000	0.000	Gamma
Off treatment full blood count rate	0.000	0.000	0.000	Gamma
Off treatment renal function test rate	0.000	0.000	0.000	Gamma
Off treatment hepatic function test rate	0.000	0.000	0.000	Gamma
Off treatment health home visitor rate	0.000	0.000	0.000	Gamma
Off treatment GP home consultation rate	0.000	0.000	0.000	Gamma
Off treatment GP surgery visit rate	0.000	0.000	0.000	Gamma
Off treatment community nurse specialist visit rate	0.000	0.000	0.000	Gamma
Off treatment district nurse rate	0.000	0.000	0.000	Gamma
On treatment consultant visit rate	0.250	0.203	0.301	Gamma
On treatment CT scan rate	0.083	0.068	0.100	Gamma

Parameter description	Mean/ Base value	Lower bound	Upper bound	Distribution
On treatment full blood count rate	0.250	0.203	0.301	Gamma
On treatment renal function test rate	0.250	0.203	0.301	Gamma
On treatment hepatic function test rate	0.250	0.203	0.301	Gamma
On treatment health home visitor rate	0.000	0.000	0.000	Gamma
On treatment GP home consultation rate	0.000	0.000	0.000	Gamma
On treatment GP surgery visit rate	0.000	0.000	0.000	Gamma
On treatment community nurse specialist visit rate	0.000	0.000	0.000	Gamma
On treatment district nurse rate	0.000	0.000	0.000	Gamma

Parameter description	Mean/ Base value	Lower bound	Upper bound	Distribution
Subsequent treatment costs				
Subsequent treatment costs surgery duration (treatment cycles)	1	0.8	1.2	Gamma
Subsequent treatment costs radiotherapy duration (treatment cycles)	3.3	2.7	4.0	Gamma
Subsequent treatment costs SACT ramucirumab (treatment cycles)	3.3	2.7	4.0	Gamma
Subsequent treatment costs SACT no ramucirumab duration (treatment cycles)	3.3	2.7	4.0	Gamma
Subsequent treatment costs surgery	1995	1604	2386	Gamma
Subsequent treatment costs radiotherapy preparation	375	302	448	Gamma
Subsequent treatment costs radiotherapy deliver	184	148	220	Gamma
Subsequent treatment costs standard chemo	3000	2412	3588	Gamma
Subsequent treatment costs ramucirumab	36000	28944	43056	Gamma
Lonsurf - Subsequent treatment proportion surgery	14%	14%	15%	Beta
Lonsurf - Subsequent treatment proportion radiotherapy	1%	1%	1%	Beta
Lonsurf - Subsequent treatment proportion SACT ramucirumab	1%	1%	1%	Beta
Lonsurf - Subsequent treatment proportion SACT no ramucirumab	18%	18%	18%	Beta
BSC - Subsequent treatment proportion surgery	16%	16%	17%	Beta
BSC - Subsequent treatment proportion radiotherapy	2%	2%	2%	Beta
BSC - Subsequent treatment proportion SACT ramucirumab	2%	2%	2%	Beta
BSC - Subsequent treatment proportion SACT no ramucirumab	17%	16%	17%	Beta

Parameter description	Mean/ Base value	Lower bound	Upper bound	Distribution
End-of-life costs				
End-of-life cost estimate	7244	5825	8664	Gamma

Parameter description	Mean/ Base value	Lower bound	Upper bound	Distribution
Societal costs				
Average hourly wage	15	12	17	Gamma
Average working hours per week	39	32	47	Gamma
% working carers	50%	40%	60%	Beta
On treatment proportion of patients who require a carer	50%	40%	60%	Beta
Off treatment proportion of patients who require a carer	50%	40%	60%	Beta
On treatment days of care required (per week)	2	2	3	Gamma
Off treatment days of care required (per week)	2	2	3	Gamma
Proportion of patients who incur transport costs	70%	55%	83%	Beta
Proportion of these patient who travel with public transport	80%	62%	93%	Beta
Cost per km	0.13	0.10	0.15	Gamma
Average distance to hospital (km)	9	7	10	Gamma
Parking cost per visit	5	4	5	Gamma

- **Key:** BSC, best supportive care; BSA, body surface area; CSR, clinical study report; CT, computed tomography; GP, general practitioner; HR, hazard ratio; km, kilometre; KM, Kaplan–Meier; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; PSA, probabilistic sensitivity analysis; SACT, systemic anti-cancer treatment; ToT, time on treatment.

Medicinrådet

Medicinrådets protokol for vurdering af trifluridin/tipiracil som monoterapi til behandling af voksne patienter med metastatisk kræft i mavesæk og mavemund (adenocarcinom) efter mindst to tidligere behandlinger for fremskreden sygdom

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner. Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser skal anbefales som mulig standardbehandling. Medicinrådet udarbejder også behandlingsvejledninger og rekommandationer for anvendelse af medicin på sygehusene. Derudover kan Medicinrådet tage andre typer sager op, der handler om medicinanvendelse.

Om protokollen

Protokollen beskriver, hvordan Medicinrådet vil foretage vurderingen af lægemidlets værdi for patienterne. Den indeholder et eller flere kliniske spørgsmål, som den ansøgende virksomhed skal besvare i deres endelige ansøgning. Til hvert spørgsmål knytter sig en definition af patientgruppen, det lægemiddel vi undersøger, den behandling vi sammenligner med og effektmålene. Udover de(t) kliniske spørgsmål indeholder protokollen også en beskrivelse af, hvordan litteratursøgning, -selektion og databehandling skal foregå. Protokollen er udarbejdet med udgangspunkt i Håndbog for Medicinrådets proces og metoder, som du kan finde Medicinrådets hjemmeside under Metoder og den ansøgende virksomheds foreløbige ansøgning, der beskriver, hvilke data der findes for lægemidlet.

Fremkommer der nye og væsentlige oplysninger i sagen af betydning for protokollens indhold, kan Medicinrådet tage protokollen op til fornyet behandling. Det samme gælder, hvis der er begået væsentlige fejl i forbindelse med sagsbehandlingen vedrørende protokollen. Hvis Medicinrådet foretager ændringer i protokollen, vil ansøgende virksomhed få besked.

Dokumentoplysninger	
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Indhold

1. Begreber og forkortelser

5-FU:	5-Fluoropyrimidin
CI:	Konfidensinterval
DECV:	Dansk Esophagus Cardia Ventrikel
EMA:	*European Medicines Agency*
EORTC:	*European Organisation for Research and Treatment of Cancer*
EPAR:	*European public assessment reports*
ESMO:	*European Society for Medical Oncology*
GRADE:	*Grading of Recommendations Assessment, Development and Evaluation System* (system til vurdering af evidens)
HR:	*Hazard ratio*
MKRF:	Mindste klinisk relevante forskel
ORR:	*Overall response rate*
OS:	*Overall Survival* (samlet overlevelse)
PFS:	*Progression free survival* (progressionsfri overlevelse)
PICO:	*Population, intervention, comparator, outcome*
PS:	Performancestatus
QLQ-C30:	*Quality of Life Questionnaire-Core* (30 spørgsmål vedr. livskvalitet til patienter med kræft)
QLQ-STO22:	*Quality of Life Questionnaire-Stomach 22* (22 spørgsmål vedr. livskvalitet til patienter med kræft i mavesækken)
RR:	Relativ risiko
S1:	*Dihydropyrimidine dehydrogenase (DPD) inhibitory fluoropyrimidine (DIF) based on a biochemical modulation of 5-fluorouracil (5-FU); S-1 contains tegafur (FF) and two types of enzyme inhibitor, 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo) in a molar ratio of 1:0.4:1.*
SAE:	*Serious adverse event*

2. Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra Servier Danmark A/S, som ønsker, at Medicinrådet vurderer trifluridin/tipiracil (Lonsurf®) som monoterapi til behandling af patienter med metastatisk kræft i mavesæk og mavemund (adenocarcinom) efter mindst to tidligere systemiske behandlinger for fremskreden sygdom. Vi modtog den foreløbige ansøgning den 2. juni 2020.

2.1 Kræft i mavesæk, mavemund og spiserør

Kræft i mavesæk (ventrikel), mavemund (gastroesophageal overgang) og spiserør (esophagus) hører samlet til den 8. hyppigste kræftform i Danmark [1]. Medianalderen for diagnosetidspunktet er for alle tre kræftformer omkring 70 år. En stor del af patienterne kan ikke tilbydes helbredende behandling, da de på diagnosetidspunktet enten har spredt sygdom eller er i for dårlig almen tilstand til at gennemgå behandling. Forekomsten af adenokarcinom i mavesæk og mavemund er steget i de senere år og er nu hyppigere end adenokarcinomer i den distale del af ventriklen. Risikofaktorer for udvikling af adenokarcinom i mavemunden omfatter refluxsygdom, Barrets øsofagus og overvægt. I Danmark håndteres patientgruppen samlet via et multidisciplinært esofagus- og ventrikelcancerteam på fire afdelinger (Rigshospitalet, Odense Universitetshospital, Aalborg Universitetshospital og Aarhus Universitetshospital).

Symptomer på kræft i mavesæk eller mavemund kommer oftest snigende. De mest almindelige symptomer er kvalme, opkastning, synkebesvær, manglende appetit eller smerter i den øverste del af maven. Vægttabet kan være betydende og nødvendiggøre ernæringsterapi, før målrettet kræftbehandling kan komme på tale. Sygdommen kan medføre blodmangel, fordi der langsomt siver blod ud fra kræftknuden. I så fald er træthed et af de første tegn på sygdommen. Smerter er et hyppigt symptom, der ofte kræver smertestillende medicin.

I 2018 blev der i Danmark registreret 1.151 nye tilfælde af patienter med kræft i spiserør, mavesæk eller mavemund ifølge Dansk Esophagus Cardia Ventrikelkarcinom (DEGC)-databasen [1]. Af disse var der 633 tilfælde af adenokarcinom i mavemunden og 237 tilfælde af adenokarcinom i mavesækken, i alt 870 patienter. Ved diagnose har ca. 40 % metastatisk kræft, svarende til ca. 350 patienter [1]. Herudover er der en gruppe af patienter med lokaliseret eller lokal-avanceret sygdom, hvor tumor ikke kan reseceres (ikke-resektabel sygdom), eller hvor patienten grundet nedsat almen tilstand eller komorbiditet ikke er operabel eller tilgængelig for kurativt intenderet, onkologisk behandling. Fagudvalget skønner, at der årligt er ca. 600 patienter, hvor kræften er inoperabel eller metastatisk, og hvor der potentielt er mulighed for pallierende, onkologisk behandling i form af kombinationskemoterapi [2]. En stor del af disse patienter er i så dårlig almentilstand eller med så betydende komorbiditet, at systemisk onkologisk behandling ikke kommer på tale [3]. Det skønnes, at ca. 300 patienter pr. år vil modtage 1.-linje, systemisk behandling med kombinationskemoterapi. Af patienter behandlet med kemoterapi med palliativt sigte er 31 % i live 1 år efter start på første systemiske behandling, ganske få er i live efter 5 år [1].

2.2 Nuværende behandling

De kliniske retningslinjer er beskrevet af Danske Multidisciplinære Cancer Grupper (DMCG) [4]. Kemoterapi forlænger levetiden og bedrer livskvaliteten og tilbydes patienter i god almentilstand med ikkekurabel sygdom i mavesæk og mavemund. Fagudvalget anslår at ca. 300 af de 600 årlige tilfælde af inoperabel eller metastatisk kræft i mavesæk og mavemund vil kunne tilbydes 1.-linjekemoterapi, mens den anden halvdel vil få tilbudt best supportive care (BSC, palliativ behandling, bestående af smerte- og symptomlindring, eventuelt på palliativ enhed eller hospice). Kemoterapibehandlingen er en kombination af et platinholdigt kemoterapeutikum (cis- eller oxaliplatin) og en antimetabolit (5-Fluoropyrimidin (5-FU), capecitabine eller S1), evt. med tillæg af taxan. Ved avanceret kræft i mavesækken er kemoterapi forbundet med en median overlevelsesgevinst på ca. 7 måneder (fra 4 til ca. 11 måneder), sammenlignet med BSC [5]. Det er vist, at kombinationsbehandling er mere effektiv end enkeltstofbehandling [5]. Kombinationskemoterapi kan dog medføre betydende bivirkninger, se nedenfor. Patienten skal fremstå i en almentilstand, hvor det skønnes, at behandlingen ikke vil medføre livsforkortende eller livskvalitetsreducerende bivirkninger. Dette betyder typisk, at patienten fremstår i performancestatus (PS) 0-2 samt uden betydelig komorbiditet. Patienter i dårligere almentilstand (PS 3-4) eller betydelig komorbiditet anbefales BSC.

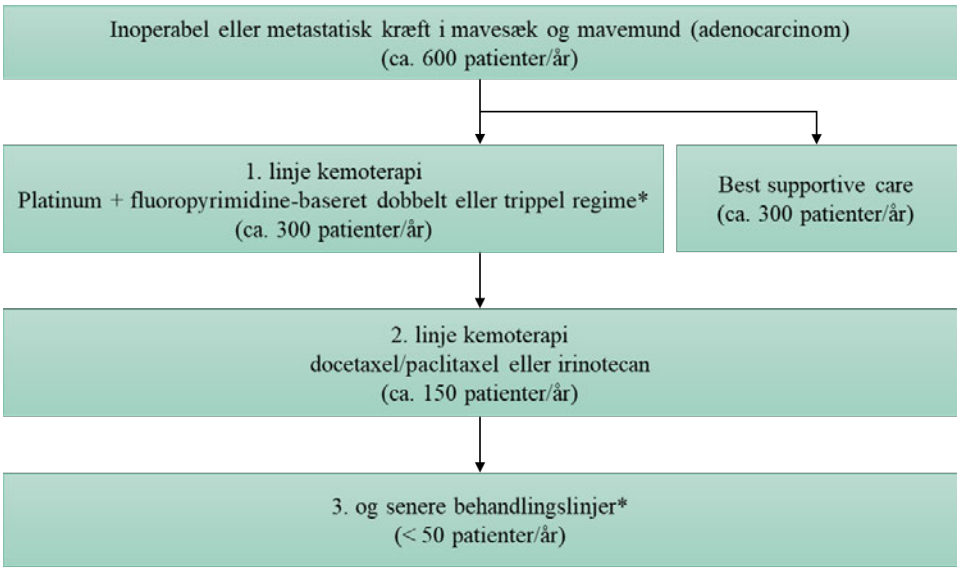
Af de ca. 300 behandlede patienter vil ca. halvdelen være i god almentilstand, når 1.-linjebehandlingen ophører med at virke, og sygdommen forværres (progression) Disse patienter er kandidater til 2.-linjekemoterapi. Baseret på mindre randomiserede ikkeregistreringsstudier består behandlingen ofte af et taxan (paclitaxel, docetaxel) eller irinotecan. Disse lægemidler er ikke godkendt til behandling af kræft i mavesæk eller mavemund i 2.-linje (off-label-anvendelse), men alle tre lægemidler har været omfattet af den tidligere anvendte danske indikation ”visse maligne lidelser” og har været anvendt i Danmark i en årrække. Paclitaxel, docetaxel og irinotecan anses som ligeværdige behandlinger til 2.-linjebehandling af kræft i mavesæk og mavemund. Den mediane overlevelse (OS) er i studier fundet til 5-6 måneder, dog i nyere randomiserede studier 7-8 måneder i den taxanbaserede kontrolarm [6–8]. Etårsoverlevelse efter start på 2.-linjebehandling er i randomiserede studier mellem 20-30 % [6–12]. Af ovenstående årsager er 2.-linjekemoterapi standard til patienter i god almen tilstand og med normalt eller let nedsat funktionsniveau [8–11,13].

Den EMA-godkendte indikation for trifluridin/tipiracil er patienter, som har modtaget mindst to forudgående systemiske behandlingsregimer for fremskreden sygdom og er kandidater til 3.-linje systemisk behandling. Samlet anslår fagudvalget, at under 50 patienter årligt vil være kandidater til trifluridin/tipiracil.

Aktuelt findes ikke godkendte 3. linjebehandlinger med veldokumenteret effekt, og de fleste patienter overgår til palliativ behandling. Hos et fåtal af patienter kan der forsøges med systemisk, antineoplastisk behandling i 3. linje. Det sker ved sekventiel anvendelse af lægemidlerne fra 2. linje, dvs. disse kan anvendes hvis de ikke tidligere har været anvendt. Det skal dog understreges, at dette ikke kan betragtes, eller i praksis fungerer, som standardbehandling, da der ikke findes dokumentation for effekten af taxaner eller irinotecan efter 2. linje.

En oversigt over anslåede årlige tilfælde pr. behandlingslinje fremgår af figur 1.

Figur 1: Oversigt over behandling for patienter med kræft i mavesæk og mavemund.



** patienter med performance status 0-1, som har mulighed for behandling i 3. linje*

Bivirkninger

Fagudvalget bemærker, at de typiske akutte bivirkninger til kemoterapi er træthed, der påvirker patienternes funktionsniveau. Kemoterapi medfører ofte kvalme, opkastninger, nedsat appetit, mundhulegener, mavesmerter eller diarré, hvilket yderligere øger risikoen for vægttab, som er et kardinalsymptom hos denne patientgruppe. Påvirkning af knoglemarven kan give nedsat immunforsvar, blodmangel og risiko for blødninger. Af mere kronisk karakter kan være risikoen for påvirkning af hørelse, nedsat nyrefunktion, nervebetændelse samt påvirkning af hjerte- og lungefunktion.

2.3 Trifluridin/tipiracil

Trifluridin/tipiracil består af en antineoplastisk thymidinbaseret nukleosidanalog; trifluridin og en thymidinphosphorylase (TPase)-hæmmer. Efter optagelse i kræftceller fosforyleres trifluridin af thymidinkinase og metaboliseres yderligere i celler til et deoxyribonukleinsyre (DNA)-substrat. Det inkorporeres derefter direkte i DNA og interfererer derved med DNA-funktionen for at forhindre celleproliferation. Trifluridin nedbrydes imidlertid hurtigt af TPase og metaboliseres let ved en første-passage-effekt efter oral indgivelse, hvorfor det gives i kombination (i samme tablet) med TPase-hæmmeren tipiracil.

Trifluridin/tipiracil doseres med 35 mg/m^2/dosis administreret oralt to gange dagligt på dag 1 til 5 og dag 8 til 12 i hver 28-dages cyklus, så længe der observeres behandlingsmæssige fordele eller indtil uacceptabel toksicitet. Dosis beregnes ud fra kroppens overfladeareal.

Denne protokol omhandler trifluridin/tipiracil med den EMA-godkendt indikation: *monoterapi til behandling af metastatisk kræft i mavesæk og mavemund (adenokarcinom) hos voksne patienter, som tidligere er blevet behandlet med mindst to forudgående systemiske behandlingsregimer for fremskreden sygdom.*

Trifluridin/tipiracil er også indiceret som monoterapi til behandling af voksne patienter med metastatisk kolorektalkræft (CRC), som tidligere er blevet behandlet med eller ikke betragtes som kandidater til tilgængelige terapier, herunder fluoropyrimidin-, oxaliplatin- og irinotecan-baserede kemoterapier, anti-VEGF-midler, og anti-EGFR-midler.

3. Kliniske spørgsmål

Medicinrådet bruger kliniske spørgsmål til vurderinger af lægemidlers værdi for patienterne. Til hvert spørgsmål knytter sig en definition af patientgruppen (population) af det lægemiddel, vi undersøger (interventionen), af den behandling vi sammenligner med (komparator(er)) og af effektmålene.

3.1 Klinisk spørgsmål 1

Hvilken værdi har trifluridin/tipiracil sammenlignet med eksisterende standardbehandling til behandling af patienter med metastatisk kræft i mavesæk og mavemund (adenokarcinom), som tidligere er blevet behandlet med mindst to forudgående systemiske behandlingsregimer for fremskreden sygdom?

Population

Voksne patienter med metastatisk kræft i mavesæk og mavemund (adenokarcinom), som tidligere er blevet behandlet med mindst to forudgående systemiske behandlingsregimer for fremskreden sygdom, og som er i god almentilstand (PS 0-1).

Intervention

Trifluridin/tipiracil: 35 mg/m^2/dosis administreret oralt to gange dagligt på dag 1 til 5 og dag 8 til 12 i hver 28-dages cyklus, så længe der observeres behandlingsmæssige fordele eller indtil uacceptabel toksicitet.

Komparator

Bedste understøttende pleje (palliativ behandling).

Effektmål

De valgte effektmål fremgår af tabel 1.

3.2 Effektmål

Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål, der er nævnt i tabel 1. For hvert effektmål har Medicinrådet fastsat en mindste klinisk relevant forskel (MKRF). Den mindste klinisk relevante forskel er den forskel mellem intervention og komparator, der som minimum skal opnås for at effektforskellen vurderes at være klinisk relevant. I det følgende afsnit argumenterer vi for valget af effektmål og de mindste klinisk relevante forskelle.

Tabel 1: Oversigt over valgte effektmål. For hvert effektmål er angivet deres vigtighed, måleenhed og mindste klinisk relevante forskel samt indplacering i de tre effektmålsgrupper (dødelighed; livskvalitet, alvorlige symptomer og bivirkninger; ikkealvorlige symptomer og bivirkninger).

Effektmål*	Vigtighed	Effektmåls-gruppe	Måleenhed	Mindste klinisk relevante forskel
Samlet overlevelse (OS)	Kritisk	Dødelighed	Medianoverlevelse	3 måneder
			Andel der fortsat er i live efter 6 måneder	5 procentpoint
Bivirkninger/uønskede hændelser	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Andel af patienter der oplever grad 3-5 uønskede hændelser	10 procentpoint
			Kvalitativ gennemgang af rapporterede bivirkninger og uønskede hændelser	Ikke relevant
Livskvalitet	Vigtigt	Livskvalitet, alvorlige symptomer og bivirkninger	EORTC-QOL-C30	10 point
			EORTC-QOL-STO22	10 point
			Median tid til forværring i performance status (PS $\geq$ 2)	3 måneder
Progressionsfri overlevelse (PFS)	Vigtigt	Livskvalitet, alvorlige symptomer og bivirkninger	Median PFS	3 måneder
			Andel der fortsat er i PFS efter 6 måneder	5 procentpoint

** For alle effektmål ønsker vi data med længst mulig opfølgningstid, med mindre andet er angivet.*

3.2.1 Kritiske effektmål

Samlet overlevelse

Forbedret samlet overlevelse med mindst mulig toksicitet er det optimale mål for kræftbehandling. Samlet overlevelse defineres som tiden fra randomisering eller behandlingsstart til død uanset årsag.

Fagudvalget betragter overlevelse som et kritisk effektmål, da kræft i mavesæk og mavemund er en livstruende sygdom. Den samlede forskel i overlevelsen i et randomiseret studie er forskellen mellem de 2 arealer under kurverne (AUC). Man kan ikke teknisk foretage en AUC-beregning på overlevelseskurver beregnet ved Kaplan Meier-metoden, før alle patienter har haft et event (død). Af denne årsag simplificeres et kurveforløb

typisk til et eller flere punktestimater - medianoverlevelsen eller ratioen mellem risiko for et event over tid i de to grupper. Disse punktestimater har derfor det forbehold, at kurverne skal have et relativt ensartet forløb. For at kompensere for dette forbehold kan medtages andre punktestimater til at beskrive kurveforløbene. I dette tilfælde anvendes udover medianoverlevelsen også overlevelsesrate efter 6 måneder.

Prognosen for patienter, der behandles i 3. linje, er dårlig. Fagudvalget anslår på baggrund af data fra EPAR, at medianoverlevelsen er under 5 måneder, og 6-månedersoverlevelsen er under 50 %. Derfor vurderer fagudvalget, at den mindste klinisk relevante forskel sammenlignet med komparator er 3 måneders medianoverlevelse og 5 procentpoint i overlevelsesraten efter 6 måneder.

Bivirkninger/uønskede hændelser

En bivirkning er en uønsket hændelse, som er vurderet at være relateret til lægemidlet. Bivirkninger ved behandling med kemoterapi ved kræft i mavesæk og mavemund kan være meget alvorlige og kan i nogle tilfælde medføre døden. Behandlingen er ikke kurativ, og det er derfor afgørende for valg af behandling, at patienterne ikke er påvirket af bivirkninger i deres resterende levetid. Derfor er bivirkninger valgt som et kritisk effektmål.

Fagudvalget ønsker en fyldestgørende oversigt over både bivirkninger og uønskede hændelser med det formål at foretage en kvalitativ gennemgang af disse. Herunder ønskes en opgørelse af andel af patienter, der oplever grad 3-5 uønskede hændelser.

Patienterne, det modtager BSC vil sjældent (aldrig) opleve grad 3-5 bivirkninger, hvorimod kemoterapi giver velkendte bivirkninger. Bivirkningerne ved behandlingen skal derfor vurderes på baggrund af den forventede effekt af behandlingen.

Fagudvalget vurderer, at den mindste klinisk relevante forskel er 10 procentpoint.

Fagudvalget vil lægge vægt på den kvalitative gennemgang af bivirkninger og uønskede hændelser, herunder alvorlighed og håndterbarhed, idet der er stor forskel på bivirkningsprofilen af henholdsvis trifluridin/tipiracil og komparator, og det kan være vanskeligt at sammenligne betydningen af de forskellige bivirkninger.

3.2.2 Vigtige effektmål

Livskvalitet

Påvirkning af livskvaliteten som følge af behandling og grundsygdom betyder meget for den enkelte patient. Den potentielle negative effekt på livskvaliteten vil ofte være afgørende for valg af behandling, særligt i en population med kort restlevetid. Det anerkendes af fagudvalget, at det er vanskeligt at måle effekten på livskvalitet af en behandling i 3. linje til patienter med kort restlevetid. Argumentet for dette er, at patienter i 3. linje ofte er svært symptomatiske, når de progredierer. Livskvalitetsmålingen kan derfor forstyrres af sygdommens naturforløb. Til trods af disse vanskeligheder vurderer fagudvalget, at livskvalitet er en vigtig faktor. Fagudvalget ønsker derfor livskvalitet opgjort som et mål for bivirkningsbyrden under behandlingen.

På grund af patienternes korte forventede levetid bør der ikke gå for lang tid, før effekten på livskvalitet måles. Derfor ønskes livskvalitet opgjort som ændring fra baseline til 1 måned efter afsluttet behandling. Livskvalitet ønskes opgjort ved to spørgeskemaer: EORTC-QOL-C30 der giver information om overordnet helbredsrelateret livskvalitet og EORTC-QOL-STO22, der omhandler livskvalitet relateret til symptomer og gener ved kræft i mavesækken.

Desuden ønskes den mediane tid til forværring i performancestatus (PS) opgjort, defineret som PS ≥ 2. Da PS er et udtryk for patientens funktionsniveau og desuden er afgørende for, hvilken behandling der kan tilbydes, anser fagudvalget det for et vigtigt supplement til vurdering af livskvaliteten. Den mindste klinisk relevante forskel vurderes at være 3 måneder.

EORTC QLQ-C30

EORTC QLQ-C30 er udviklet til at måle livskvaliteten hos patienter med kræft. EORTC QLQ-C30 er et spørgeskema med 30 spørgsmål og i alt 15 domæner, herunder fem funktionsskalaer, tre symptomskalaer, seks enkeltstående symptomer/omstændigheder og en global livskvalitetsscore [14]. Der anvendes en scoringsskala fra 0-100 (en høj score angiver et højt funktionsniveau). Resultatet af to af de 30 spørgsmål udgør den globale livskvalitetscore. En ændring i 10 point fra baseline anses for klinisk relevant for patienter med fremskreden kræft [15][16][17]. Den mindste klinisk relevante forskel er derfor sat til 10 points forskel for trifluridin/tipiracil sammenlignet med komparator.

EORTC QLQ-STO22

EORTC QLQ-STO22 er udviklet som et supplement til EORTC QLQ-C30 [18]. Spørgeskemaet indeholder 22 spørgsmål og er udviklet til patienter med kræft i mavesækken, der varierer i sygdomsstadium og behandlingsmodalitet. Der anvendes en scoringsskala fra 0-100 (en høj score angiver et højt niveau af symptomer). Da dette spørgeskema er et supplement til EORTC QLQ-C30, og der anvendes samme scoringsskala, defineres den mindste klinisk relevante forskel også som 10 point for dette spørgeskema.

Progressionsfri overlevelse (PFS)

Fagudvalget anser PFS som et vigtigt effektmål til vurdering af den periode, hvor patienterne har det bedre, efter de har modtaget 3.-linjebehandling. PFS kan således give en anden information end overlevelse. Den tid, der går uden sygdomsprogression, vil typisk være præget af stabilitet eller bedring i symptomerne, herunder færre smerter og gener og bedre funktion, hvilket har stor indflydelse på patientens dagligdag og livskvalitet. PFS afspejler således byrden af symptomer samt varigheden af denne periode og kan dermed anses som et surrogatmål for respons. PFS inddrager dog også tidsaspektet.

PFS ønskes opgjort som median i antal måneder samt PFS-rate efter 6 måneder. Som nævnt ovenfor er prognosen for disse patienter meget dårlig. Fagudvalget anslår, at median-PFS for patienter, som modtager bedste understøttende behandling, er < 3 måneder, og stort set alle patienter vil progrediere eller dø indenfor 6 måneder. Fagudvalget vurderer, at den mindste klinisk relevante forskel sammenlignet med komparator er 3 måneders median PFS og 5 procentpoints forskel i andel patienter i PFS efter 6 måneder.

4. Litteratursøgning

Medicinrådet har på baggrund af den foreløbige ansøgning undersøgt, om der findes et eller flere studier, hvor trifluridin/tipiracil er sammenlignet direkte med de valgte komparatorer.

Medicinrådet har fundet følgende studie, som indeholder en direkte sammenligning mellem trifluridin/tipiracil og komparator:

- **TAGS-studiet: TAS-102-302; NCT02500043**

Det er tilstrækkeligt datagrundlag til at besvare det kliniske spørgsmål. Ansøger skal derfor ikke søge efter yderligere fuldtekstartikler, men skal konsultere Det Europæiske Lægemiddelagenturs (EMA) European public assessment reports (EPAR) for både det aktuelle lægemiddel og dets komparator(er).

5. Databehandling og -analyse

Ansøger skal bruge Medicinrådets ansøgningsskema til sin endelige ansøgning. Vær opmærksom på følgende:

Studier og resultater

- Beskriv de inkluderede studier og baselinekarakteristikken af studiepopulationerne. Herunder ønskes en redegørelse for hvilke behandlinger patienterne i studierne har fået tidligere.
- Angiv hvilke studier/referencer der er benyttet til at besvare hvilke kliniske spørgsmål.
- Brug som udgangspunkt ansøgningsskemaet til ekstraktion af al relevant data.
- Krydstjek de ekstraherede data med de resultater, der fremgår af de relevante EPARs.
- Angiv årsager, hvis der er uoverensstemmelser mellem resultaterne fra artikler og EPARs.
- Angiv årsager, hvis der er uoverensstemmelser i forhold til PICO mellem protokollen og studierne.
- Vurdér, hvordan uoverensstemmelserne påvirker estimaterne.

Statistiske analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Udfør en komparativ analyse for hvert enkelt effektmål på baggrund af de ekstraherede data.
- Hvis data for et effektmål ikke er baseret på alle deltagere i et studie, skal ansøger ikke gøre forsøg på at erstatte manglende data med en meningsfuld værdi.
- Angiv for hvert effektmål og studie, hvilken analysepopulation (f.eks. intention to treat (ITT), per-protocol) der er anvendt.

- Angiv en sensitivitetsanalyse baseret på ITT-populationen, hvis den komparative analyse ikke er baseret herpå.
- Angiv for hvert effektmål og studie, hvilken statistisk analysemetode, der er anvendt.
- Basér de statistiske analyser for dikotome effektmål på den relative forskel.
- Beregn den absolutte forskel med udgangspunkt i den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen (jævnfør Appendiks 5 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).

Vær opmærksom på, at Medicinrådets sekretariat forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans, uanset valg af analysemetode.

6. Evidensens kvalitet

Medicinrådet anvender GRADE (Grading of Recommendations, Assessments, Development and Evaluation) til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Evidensens kvalitet angiver, i hvor høj grad vi kan have tiltro til den evidens, vi baserer vurderingen af lægemidlets værdi på.

7. Andre overvejelser

Fagudvalget ønsker, at ansøger belyser, hvorvidt der er en forskel på effekten afhængigt af, hvilken tidligere behandling patienten har fået (irinotecan eller taxan).

Fagudvalget ønsker, at ansøger indsender opdaterede overlevelsesdata (baseret på et senere data cut-off i det identificerede studie), hvis det er muligt. Såfremt disse data er upublicerede, vil Rådet tage stilling til, hvorvidt de kan inddrages som evidensgrundlag i vurderingen af trifluridin/tipiracil.

8. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning på området.

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10. Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende kræft i mavesæk og mavemund	
Formand	***Indstillet af***
Lene Bæksgaard Jensen Overlæge	Lægevidenskabelige Selskaber
Medlemmer	***Udpeget af***
Mette Karen Nytoft Yilmaz Overlæge	Region Nordjylland
Marianne Nordsmark Overlæge	Region Midtjylland
Helle Anita Jensen Overlæge	Region Syddanmark
Kenneth Hofland Overlæge	Region Sjælland
Jon Kroll Bjerregaard Overlæge	Region Hovedstaden
Natalia Marta Luczak Farmaceut	Dansk Selskab for Sygehusapoteksledelse
Zandra Ennis Læge	Dansk Selskab for Klinisk Farmakologi
Mikkel Eld Overlæge	Dansk Patologiselskab
En patient/patientrepræsentant	Danske Patienter

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11. Versionslog

Version	Dato	Ændring
1.0	24. november 2020	Godkendt af Medicinrådet.

Medicinrådet

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